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ARACHNODACTYLY (SPIDER FINGERS)

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Nearly half a century ago there appeared the first report (Marfan, 1896)[1] on a developmental anomaly which was well described as a congenital deformation of the four extremities characterized by long and slender bones. The names applied to the condition have been: spider fingers, arachnodactyly or arachnodactylia, dolichostenomelia, and hyperchondroplasia (by way of contrast with achondroplasia). Subsequently other congenital disabilities have been associated: dislocation of the lens, cardiac defects and feeblemindedness. More than 200 cases are said to have been reported in the literature, and the condition is indeed not rare, since 4 patients have been called to my attention by members of the staff within the last two years. Judging by a survey of a dozen reports in print,[2] one is surprised by the scarcity of anthropologic measurements, since these would certainly permit the earlier and more accurate recognition of cases now clinically missed. In some of the reports of cases the diagnoses were not warranted by the measurements given; in many of the cases the measurements were fragmentary, perhaps only of one finger or even of one phalanx, and, finally, in most cases the landmarks used were so obscure as to prevent comparisons by the reader. Some sounder evidence, partly computed from observations in the literature but mainly from my own observations, together with the more notable clinical complications, will now be presented systematically from the aspect of the build of the patient.

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From the Department of Medicine, Stanford University School of Medicine.

1. Marfan, A. B.: Un cas de déformation congénitale des quatre membres, plus prononcée aux extrémités, caractérisée par l'allongement des os avec un certain degré d'amincissement, Bull. et mém. Soc. méd. d. hôp. de Paris **13**:220 (Feb. 28) 1896.

2. (*a*) Mery, H., and Babonneix, L.: Un cas de déformation congénitale des quatre membres: Hyperchondroplasie, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:671 (July 4) 1902. (*b*) Achard, C.: Arachnodactylie, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:834 (Oct. 10) 1902. (*c*) Börger, F.: Ueber zwei Fälle von Arachnodaktylie, Ztschr. f. Kinderh. **12**:161, 1915. (*d*) Young, M. L.: Arachnodactyly, Arch. Dis. Childhood **4**:190 (Aug.) 1929. (*e*) Weve, H.: Ueber Arachnodaktylie, Arch. f. Augenh. **104**:1 (May) 1931. (*f*) Huber, J.; Lièvre, J. A., and Hector: Arachnodactylie, Bull. Soc. pédiat. de Paris **35**:49 (Jan. 19) 1937. (*g*) Roederer, C.: Un cas d'arachnodactylie, ibid. **35**:225 (April 20) 1937. (*h*) Roch, M.: Arachnodactylie, Presse méd. **45**:1429 (Oct. 9) 1937. (*i*) Olcott, C. T.: Arachnodactyly (Marfan's Syndrome) with Severe Anemia, Am. J. Dis. Child. **60**:660 (Sept.) 1940. (*j*) François, J.: De la pathogénie et de l'origine hypophysaire du syndrome de Marfan, Bull. et mém. Soc. franç. d'opht. **48**:157 (May 13) 1935. (*k*) Roederer, C.: Un cas larvé de dolichosténomélie, Bull. Soc. pédiat. de Paris **36**:269 (April 26) 1938. (*l*) Marfan.[1]

REPORT OF CASES

CASE 1 (Joe G.).—*Family History.*—Arachnodactyly was not known to be present in the grandparents, the parents or the five siblings, who ranged in age from 12 down to 4 years. Similar statements are common about reported cases but should be regarded skeptically; more than once 4 instances in the same family have been reported (Weve, 1931)[2e]; hence it is probable that a number of the instances in the literature stated to be isolated could have been demonstrated to be really familial if measurements had been made of the immediate relatives. However, I have not had the opportunity to record these measurements for the 4 new cases.

Personal History.—This boy, the third among six children of a Dalmatian mother and a Portuguese father, was born Dec. 1, 1933 and was 10 years old when he was studied in Stanford University Hospital. There was no peculiarity about pregnancy or birth. His birth weight was 9 pounds (4,082 Gm.). Also his hands, feet and ears were noticed at once as large, and the nurses called him "infant Hercules."

At 1 year his difficulty in seeing was noticed, and this deficiency has progressed and is now the chief complaint. Early in his infancy the frailness of the musculature was observed. At 5 he had to have special shoes, partly because of the length but mainly because of the extraordinary narrowness of his feet. At 6 he entered school, where he has been cooperative and is now, with some outside help from the teachers, in the fourth grade. At 7 he had some kind of disorder of the kidneys which vanished within a year.

Examinations.—The physical and neurologic examinations were made by Dr. Frederick A. Fender, who referred the patient to me for a study of his build. Little was found amiss. The patient appeared of normal intelligence. There was underdevelopment of the biceps, triceps and of the muscles of the forearms, thighs and calves. There was slight ataxia on the finger to nose test bilaterally. The biceps and triceps reflexes were absent.

The psychologic examination was made by Dr. Hale Shirley, who reported that the intelligence quotient was 90 and was reasonably accounted for by the difficulty in vision.

The urine was normal.

The examination of the eyes by Dr. Jerome W. Bettman revealed that the chief complaint was nearsightedness which had been present from infancy. External inspection revealed noticeable smallness of the pupils, probably congenital. Such miosis is a part of the syndrome found in association with dislocated lenses and arachnodactyly. Severe iridodonesis (tremulous movements of the iris), pathognomonic of subluxation, dislocation or absence of the lens, was noted in each eye. As the pupils did not dilate well with homatropine hydrobromide cycloplegia, careful examination of lenses and fundi was carried out with difficulty. The lenses were subluxated and still in the patellar fossa. The optic disks and surrounding areas appeared to be within normal limits. With uncorrected vision Joe was able to count fingers at 6 feet (1.8 meters) with the right eye and at 8 feet (2.5 meters) with the left eye. Retinoscopy with homatropine cycloplegia disclosed between 20 and 25 diopters of myopia in each eye. Correction of the refractive error improved the vision only to the extent

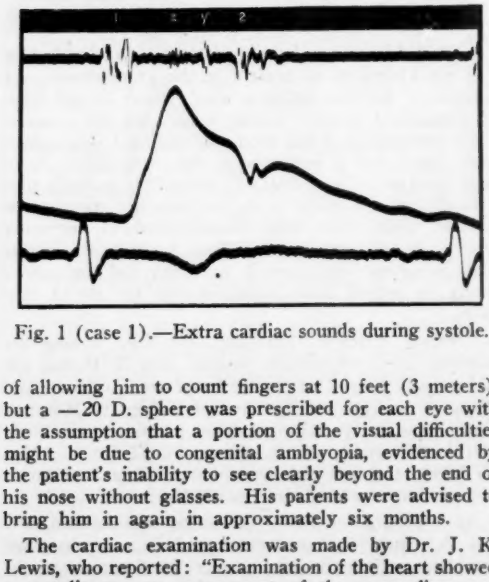

Fig. 1 (case 1).—Extra cardiac sounds during systole.

of allowing him to count fingers at 10 feet (3 meters), but a —20 D. sphere was prescribed for each eye with the assumption that a portion of the visual difficulties might be due to congenital amblyopia, evidenced by the patient's inability to see clearly beyond the end of his nose without glasses. His parents were advised to bring him in again in approximately six months.

The cardiac examination was made by Dr. J. K. Lewis, who reported: "Examination of the heart showed a systolic murmur over most of the precordium and within the apex a pair of extra sounds during systole. Roentgenograms of the heart showed it to be normal in shape and at the upper limit of normal size. A diagnosis of the type of lesion could not be made." These extra cardiac sounds are put on record in figure 1.

This topic is being further studied by Dr. D. A. Rytand. With regard to cardiac function, it may be added that the boy plays actively and has never had cyanosis or edema.

CASES 2, 3 and 4.—Clinically these 3 patients showed no ocular or cardiac defects but were called to my attention by Dr. Lloyd B. Dickey. The patient in case 2, Kathleen S., aged 13, was measured by him. The measurements of the patients in case 3, Louis M., aged 13, and case 4, Loraine B., aged 6, were made by me from roentgenograms or taken from the records of the pediatric department. The observations on these 3, being partial, are merely shown in some of the tables and discussed incidentally. Most of what follows will refer to the patient in case 1, Joe G.

ARACHNODACTYLY AND OTHER ASPECTS OF BUILD

Inspection.—Besides the points already noted, the patient, Joe, showed a funnel depression at the lower end of the sternum, as has been reported in earlier cases. The distribution of hair and of fat and the penis and testes were all normal

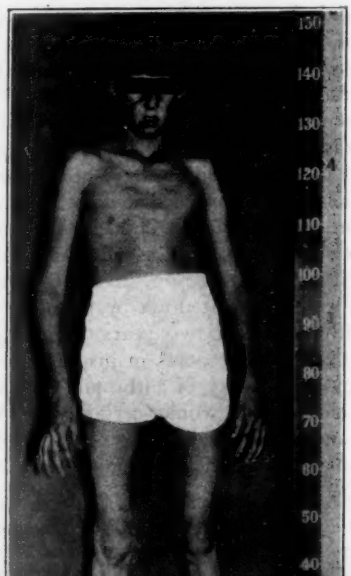

Fig. 2 (case 1).—General appearance of the patient.

enough. His general appearance is shown in figure 2.

Methods of Measurement.—All measurements were made on the naked patient. The landmarks and technic follow anthropologic authorities, but, as even they differ in certain items, the specifications are recorded. The body and head were measured by the method of Hrdlička,[3] except for the head height, which was done with Todd's head spanner. All details may be found in earlier

3. Hrdlička, A.: Anthropometry, ed. 1, Philadelphia, Wistar Institute of Anatomy and Biology, 1920, pp. 79-81; ed. 2, 1939, p. 97.

publications (Gray and Ayres, 1931):[4] special circumferences (Bayer and Gray, 1934),[5] hand (Bayer and Gray, 1933),[6] arm, foot, leg and segments (Kaslow and Gray, 1941,[7] Gray, 1941)[8] and foot breadth (Hrdlička, 1920, 1939[8] and Gray, 1937).[9]

Normal Standard.—The choice of a standard of reference with which to compare a patient of peculiar build is apt to be controversial. In this instance one would wish a standard based on boys aged 10 years, the offspring of Portuguese fathers and Dalmatian mothers, brought up under the conditions of life on a fruit ranch in Santa Clara County. No such standard is available. I shall use a standard based on measurements of 173 boys aged between 9.5 and 10.5 years, of mixed racial stocks, mostly third generation native born. Their economic status was higher than the patient's, but his was not at all impoverished, inasmuch as he was brought to the hospital as a private, not a ward, patient. Furthermore, the standard was based on our own observations (Gray and Ayres, 1931)[4] and therefore corresponds precisely as to technic. Since private school children are notably tall and slender for their age, their standard is more appropriate than might be thought at first, because it is less likely than most standards to exaggerate the unusual tallness and slimness of the patient. This standard will be referred to hereafter as the norm. For the other cases to be discussed, various standards were used but will be omitted here.

Methods of Interpreting the Measurements.—The measurements will be displayed in several tables. For the sake of the reader, however, only the more significant items will be selected for discussion. Occasionally the absolute values will be emphasized, but for the most part the patient's dimensions will be related to the norm. In order to avoid tedious repetition, the following expressions will be used repeatedly, and are therefore now specified:

1. Absolute measurement, mainly in millimeters (table 1).

2. Relative measurement, as a percentage of stature.

3. Segment proportion, the proportion which a member such as the hand bears to the whole extremity such as the total upper extremity from the acromion to the tip of the midfinger.

4. Rank or percentile, the position of the patient among 100 normal boys of his age. This rank will be a most useful expression to the reader throughout the text. The method of calculation is that usual in statistical work and will therefore be omitted, save for a single explanation for any one who may wish the detail.

TABLE 1.—*Routine Data on the Build of Patient Joe G., Case 1* *

Measurement		Absolute in Millimeters	Relative in Percentage of Stature
Stature	S	1,545	100.0
Sitting height	Si	763	49.4
Chest circumference	C	684	44.3
Transverse	T	246	15.9
Anterior posterior	AP	156	10.1
Module	Chm	201	13.0
Shoulder biacromial	BA	320	20.7
Pelvis bicristal	BC	277	17.9
Head length	L	183	11.8
Breadth	B	148	9.6
Height	OH	122	7.9
Module	CM	151	9.8
Face height	MN	108	7.0
Breadth	BZ	128	8.3
Module	FM	118	7.6
Nose height	NH	48	3.1
Breadth	NB	28	1.8

* Weight (W) in kilograms is 35.0; in relation to stature in centimeters, 22.7.

Body and Head.—The set of dimensions for routine study of build and growth, as picked from the vast number available in the physical anthropologic authorities, was used in our first monograph, in 1931,[4] and still proves satisfactory. For this patient, these are put on record in table 1.

COMMENT

His weight in absolute terms (kilograms) was practically normal for his age. If it is related to his tall stature, however, by computation of a weight-stature index (W [Kg.] S [cm.]), it is found that his relative weight is low, nearly down to the twenty-ninth percentile; that is to say, 29 per cent of boys of his age would be still thinner. (Following is the method of computation: His weight-stature index is 22.7. The normal index for boys of 10 years [given in the

4. Gray, H., and Ayres, J. G.: Growth in Private School Children, with Averages and Variabilities Based on 3,110 Measurings on Boys and 1,473 on Girls, Chicago, University of Chicago Press, 1931, chap. 3, p. 90.

5. Bayer, L. M., and Gray, H.: Anthropometric Standards for Working Women, Human Biol. **6**:472 (Sept.) 1934.

6. Bayer, L. M., and Gray, H.: The Hand: Method of Measurement, Am. J. Phys. Anthropol. **17**:379 (Jan.-March) 1933.

7. Kaslow, A. L., and Gray, H.: Segment-Proportions in the Extremities, with Special Reference to Tall Men and Giants, Growth **5**:385 (Dec.) 1941.

8. Gray, H.: Leg-Length: A Survey of Methods Together with New Conversion Equivalents, Growth **5**:373 (Dec.) 1941.

9. Gray, H.: The Minneapolis Giant, Ann. Int. Med. **10**:1669 (May) 1937.

table in our monograph] is 24.4; hence his index is 1.7 below normal [22.7 — 24.4 = — 1.7]. This deviation divided by the standard deviation [3.1], the conventional unit for assessing deviation, equals — 0.55 [— 1.7 ÷ 3.1 = — 0.55]. When this value for x/σ is referred to a probability table, the patient's percentile rank is found to be 29.1).

His height is above the mean by 13 cm. (5.1 inches), this deviation putting him nearly up to the 99 percentile; that is, only 1 per cent of boys of his age would be expected to be taller. Hence, he is extremely tall but not a giant.

The bicristal width of the pelvis, 277 mm., was most extraordinary and was therefore remeasured the next day with a different pair of calipers, by way of confirmation. The relative value of bicristal width to stature (BC/S) was 17.9 per cent. Both these values, absolute and relative, are larger than those shown by any of the 173 normal controls aged 9.5 to 10.5 years, and even larger than those of any one of the next older group of normal controls, 201 boys between 10.5 and 11.5 years. Even in our normal girls, the magnitude 277 mm. was not reached as an average until the group of girls aged 17.5 to 18.5 years. Whether the patient's pelvis was feminine in other respects was not studied. His genitalia, as remarked already, were not particularly small.

The biacromial diameter or shoulder breadth was, on the contrary, narrow. The relative value of the biacromial width to the stature (BA/S) set his position at the 19 percentile; that is, 19 per cent of normal boys would probably be even more narrow-shouldered.

The rest of the dimensions of his body and head will be most easily grasped by the reader when presented in relative terms as percentages of stature or as the patient's position in rank among his fellows. Thus, the transverse diameter of the chest in relation to the stature (T/S) at 15.9 per cent of stature was normal, which put him practically on the 50 percentile. All the remaining relative dimensions were smaller than normal and placed the patient in progressively lower rank; relative weight at 29 percentile, shoulder breadth and nose height at 19, chest circumference at 16, then anteroposterior chest depth, head breadth and bizygomatic breadth of face at 7 and mentonasion face length at 6. The remainder placed him at lower than the 1 percentile; that is, fewer than 1 boy in 100 would have as low a measurement as the patient. These items were relative sitting height, relative head length, relative head height and relative nose breadth. There is, in short, distinct evidence of microcephaly, apparently a new finding in connection with arachnodactyly.

The indexes in table 2 may now be considered. The amazing one is the trunk breadth index, bicristal to biacromial (BC/BA), 86.6 per cent. This disproportion between the upper and lower ends of the trunk is so rare as to occur, I believe, less often than once in a thousand persons, and probably even less than that. The other

TABLE 2.—*Routine Indexes for Patient Joe G., Case 1*

Index		Percentage
Chest	AP/T	63.4
Transverse breadth	BC/BA	86.6
Cephalic	B/L	80.9
Face	MN/BZ	84.4
Face/head length	MN/L	59.0
Face/head breadth	BZ/B	86.5
Nose	NB/NH	58.3

indexes worthy of comment are slenderness of the nose, the nasal index or breadth to height (NB/NH), 58.3 per cent, which put the patient at the 12 percentile rank; and the flat chest index, anteroposterior to transverse (AP/T), 63.4, a figure which placed the patient at the 4 percentile rank.

Girths of the Extremities.—The measurements, both absolute and relative, are shown in table 3,

TABLE 3.—*Girths of Extremities*

Extremity	Norm* (1)	Joe (2)	Ratio (3) (2)/(1)
	Absolute Measurement		
	Mm.	Mm.	
Thigh.....Tg	405	372	0.92
Calf.....Cf	283	232	0.82
Upper arm.....UA	202	188	0.93
Forearm.....LA	208	184	0.88
		Average	0.89
	Measurement in Relation to Stature		
	Per Cent	Per Cent	
Thigh.....Tg/S	26.7	24.1	0.90
Calf.....Cf/S	18.7	15.0	0.80
Upper arm.....UA/S	13.3	12.2	0.92
Forearm.....LA/S	13.7	11.9	0.87
		Average	0.87

* The nearest norm for boys of average stature, 1,515 mm., may be found in Martin,[10] page 292.

together with some standards taken as the nearest approach (Martin).[10] It is plain that our patient has remarkably slender muscles. For these items no ranks can be stated, because no standard deviations are at hand.

10. Martin, R.: Lehrbuch der Anthropologie, ed. 2, Jena, Gustav Fischer, 1928, vol. 1, pp. 390, 396-399, 419 and 421.

Hand and Fingers.—The data are in table 4. The measurements on the patient were made partly on the living hand, partly on an outline tracing and partly on a roentgenogram of the left hand. They are therefore quite accurate and do by way of comparison seems to be to take the various items related to stature and to compare these relative measurements with the relative measurements of such normal controls as are available. The remarkable features are the

TABLE 4.—*Hand Measurements*

		Joe G. Age: 10.1 Years				Kathleen S. Age: 13.1 Years				Louis M. 13.6 Years	Loraine B. 6 Years
		Absolute in Mm.	Relative in Percentage of Stature	Norm in Percentage of Stature	Ratio (4)/(5)	Absolute in Mm.	Relative in Percentage of Stature	Norm in Percentage of Stature	Ratio (8)/(9)	Mm.	Mm.
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Ray I = thumb	I	137	8.9	8.0	1.11	153	9.4	7.8	1.21	123	95
Ray II = index	II	179	11.6	10.6	1.09	198	12.2	10.5	1.16	166	129
Ray III = hand L	HL	186	12.0	11.1	1.08	206	12.7	11.0	1.15	171	130
Ray IV = ring	IV	181	11.7	10.5	1.12	195	12.0	10.4	1.15	163	122
Ray V = little	V	159	10.3	9.1	1.13	165	10.2	9.1	1.12	138	104
Finger length III	FL	95	6.2	5.5	1.12	...	....	....	....	87	00
Palm length	PL	91	5.9	5.5	1.07	...	....	....	....	84	70
Hand breadth	HB	72	4.7	5.0	0.93	78	4.8	5.0	0.96	80	54
Bistyloid breadth	Bs	48	3.1	3.4	0.91						
Hand circumference (mc)	HC	171	11.1	11.9	0.93						
Palm circumference (max.)	PC	175	11.3	12.5	0.91						
Wrist circumference (min.)	Wr	130	8.4	9.6	0.88						
				Mm.	(3)/(5)			Mm.	(7)/(9)		
Stature in mm	S	1,545	....	1,415	1.09	1,626		1,617	1.01	1,529	1,181
			In Ratio to Stature in Cm.				In Ratio to Stature in Cm.				
		Kg.			(4)/(5)	Kg.			(8)/(9)	Kg.	Kg.
Weight	W	35.0	22.7	24.4	0.93	46.8	28.8	31.6	0.91	34.7	15.2

TABLE 5.—*Segmental Proportions*

	Joe G.			Kathleen		Louis		Loraine		Name Not Stated (Mery)[2a] (Francois)[2j]	
	Absolute in Mm.	Relative in Percentage of Stature	Ratio of Relative Measurement to That of Normal Control	Absolute in Mm.	Ratio of Relative Measurement to That of Normal Control	Absolute in Mm.	Ratio of Relative Measurement to That of Normal Control	Absolute in Mm.	Ratio of Relative Measurement to That of Normal Control	Ratio of Relative Measurement to That of Normal Control	Ratio of Relative Measurement to That of Normal Control
Hand length.....da-ca	186	12.0	1.08	...	....	...	....	...	....	1.12	
Radius length.....r-ca	250	16.2	1.08	...	....	...	....	...	....	1.15	
Humerus length....ac-r	293	19.0	1.02	...	....	...	....	...	....	1.18	
Total arm length...ac-da	729	47.2	1.06	...	....	...	....	...	....	1.15	
Foot length.....ap-pt	260	16.8	1.12	254	1.05	234	1.02	167	....	1.16	1.03
Shank.....ti-sph	380	24.6	1.16	...	....	...	....	...	....	1.11	1.37
Thigh.....in-ti	425	27.5	1.20	...	....	...	....	...	....	0.99	1.24
Cumulated leg.....	1,065	68.9	1.16	...	....	...	....	...	....	1.08	1.23
Foot breadth.....mt	75	4.8	0.84	76	0.86	85	0.98	56			
	Percentage			Percentage		Percentage					
Foot index.....FB/FL	28.8	....	0.79	29.9	0.83	36.3	0.96	33.5	0.92		
Hand index.....HB/HL	38.7	....	0.86	37.9	0.82	46.8	1.05	41.5			

quite complete and are, I believe, the smallest number of items suitable to a proper study of the size and shape of the hand.

The patient's rank cannot be estimated because of lack of standard measures of variability for this little studied trait in man. The best I can

length of the patient's hand as a whole, the length of the five so-called rays (a better unit than finger length) and the slenderness of the hand.

The relative hand length, 12 per cent of the stature, is most exceptional, being entirely outside any values I have found in normal people

and lying among the values for giants as shown in the diagram in my paper on the Minneapolis giant (Gray, 1937).[9] A convenient figure to hold in mind for the normal hand is about 11 per cent of stature. The comparison may be expressed as the ratio of patient to norm, according to the values from table 4, as 12.0 divided by 11.1 = 1.08, or 8 per cent in excess of normal.

The hand index at the foot of table 5, hand breadth to hand length (HB/HL), gives the ratio 72 to 186, or 38.7 per cent. This may be compared with the index computed from the averages for hand length and breadth for our 16 tall normal controls (Kaslow and Gray, 1941), which was 45. Taking the ratio patient to norm, one has 38.7 to 45.0, or 0.86, or 14 per cent narrower than expectation. Or the patient's index may be compared with the lowest index given (Martin)[10] for Europeans, namely Frenchmen at 42.7. Against this standard, the patient's slenderness is not so obvious but is still very definite.

Fig. 3 (case 1).—Hands of the patient.

TABLE 6.—*Hand Length in Percentage of Stature (Relative Hand Length, HL/S); Some Cases From the Literature*

Observer	Patient	Sex	Age	HL/S	Ratio *
Roch.....1937	Name not stated	F	29	13.8	1.26
Case 2.....1944	Kathleen	F	13	12.7	1.15
Borger....1915	H. G.	M	9	12.0	1.15
Francois..1935	Name not stated	M	12	12.3	1.14
Mery.....1902	Gabrielle	F	11	12.4	1.12
Case 1.....	Joe	M	10	12.0	1.08
Marfan...1896	Gabrielle	F	5	11.7	1.07
Roederer..1938	Name not stated	F	13	10.9	1.03
Case 4.....	Loraine	F	6	11.0	1.02
Case 3.....	Louis	M	13	11.2	1.01

* Ratio of relative measurement of patient to that of normal control.

Foot.—The relative foot length in table 5 is 16.8 per cent of stature, which may be compared with the relative foot length in our 16 tall controls at 15 per cent, or a ratio patient to norm of 1.12, or 12 per cent longer than expectation. The relative foot length taken here as standard may be carried in mind as agreeing with the run of values for sundry series in Martin's textbook. But even if one should take his most extreme figure for Europeans, 16.0 per cent of stature, the patient is still longer footed. From the viewpoint of slenderness, next, let us consider his foot index of breadth to length (B/L) of 28.8 per cent against the lowest index given (Martin) for boys, namely 38.4, from which is obtained the ratio patient to norm of 0.75, or 25 per cent slenderer than expectation. This is certainly an amazing foot.

Fig. 4 (case 1).—Feet of the patient.

TABLE 7.—*Foot Length in Percentage of Stature; Some Cases from the Literature*

Observer	Patient	Sex	Age	FL/S	Ratio *
Mery.....1902	Gabrielle	F	11	17.6	1.16
Case 1.....	Joe	M	10	16.8	1.12
Roch.....1937	Name not stated	F	29	16.3	1.10
Borger....1915	K. D.	F	1	16.4	1.09
Borger....1915	H. G.	M	9	15.8	1.05
Case 2.....	Kathleen	F	13	15.6	1.05
Marfan.....	Gabrielle	F	11	16.2	1.04
Francois.....	Name not stated	M	12	15.5	1.03
Case 4.....	Loraine	F	6	14.1	1.02
Case 3.....	Louis	M	13	15.3	1.01

* Ratio of relative measurement of patient to that of normal control.

Segment Proportions in the Extremities.—From these relations between limb length and

body length (stature), one must now distinguish the proportions between each of the three segments as against the total limb. This segmental viewpoint has been little documented in the literature; nevertheless, it is worth study (*a*) for pure science, (*b*) for possible use in estimating fitness for particular sports or particular occupations and (*c*) for diagnosis of abnormalities of growth, such as dwarfism or partial gigantism. A beginning in this direction was made in an earlier paper with reference to tall normal men and giants (Kaslow and Gray, 1941).[7]

Pursuing this approach, with reference to the special form of partial gigantism called arachnodactyly, a ratio may be made between each segment proportion for the patient and the corresponding normal segment proportion as near as I have been able to estimate it. The computations discussed in the following paragraph in percentages of limbs are not tabulated in table 5; but, as a matter of record for comparison with the literature, which is more apt to state segments in percentages of stature, the more important data are so presented. One finds, then, that the patient's value for the hand (specifically, hand length from dactylion to carpale [da-ca] divided by total arm length of acromion to dactylion [ac-da]) to be in ratio to the normal value as 1.06 : 1, that is, 6 per cent longer; for the radius to be 1.01 : 1, that is, 1 per cent longer, and for the humerus to be 0.96 : 1, that is, 4 per cent shorter. In other words, the tentative implication is that arachnodactyly manifests a partial gigantism in the upper limb which is not of like degree in the three segments, but is progressively more pronounced as one proceeds away from the body.

For the lower extremity, however, surprisingly enough the reverse is found, since the inordinate length is less noticeable distally. The details follow. The patient's value for the foot is to the normal value in the ratio of 0.86 : 1, that is, 14 per cent less; for the shank in the ratio 1.04 : 1, that is, 4 per cent longer; for the thigh in the ratio 1.20 : 1, that is, 20 per cent longer.

If another comparison is tried, by using as working unit the proportion of segment to stature, as in table 5, one finds confirmation both for arm and for leg segments. That is, in the arm the disproportion is more pronounced distally, whereas in the leg the disproportion is more pronounced centrally.

In connection with the hypothesis in the literature that this condition presents the opposite of achondroplasia, the segments should prove to be proportionately longer, the farther from the trunk they are. Evidence so far is equivocal. Discrepant findings for the two extremities are not solved by the few pertinent figures which I have found in the literature and have translated into ratios and shown in the last columns in table 5. For the paradox in the two extremities, then, I see no immediate explanation. It is to be remembered, however, that the technic of leg measurement, especially of the thigh segment, is more difficult than that for the measurements of the segments in the arm; and this difficulty may even cause unreliable observations.

SUMMARY

A 10 year old boy presented the rare anomaly arachnodactyly, or spider fingers, together with congenital dislocation of the lenses and a congenital cardiac peculiarity. A new contribution to the knowledge concerning this anomaly was made through a careful study of physical build by means of anthropologic measurements.

PRIMARY ATYPICAL PNEUMONIA OF UNKNOWN CAUSE

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Primary atypical pneumonia, or viral pneumonia, is not a new disease but has come into prominence because of its probable increased incidence, its lack of response to sulfonamide drugs and the more generalized use of roentgen therapy. The morbidity of this disease is at the present time four times that of the pneumococcic lobar type of pneumonia.[1] According to reports of the United States Army, the incidence of the disease is about 20 to 25 per cent of that of all infections of the respiratory tract [2] and above 50 and perhaps as high as 75 to 80 per cent of that of all pulmonary lesions.[3] In the United States Navy the morbidity exceeds the figure for 1942, which was 2.79 per thousand.[4] The loss of time in 738 cases in the air corps amounted to 20,000 man days, or 55 man years.[5]

EPIDEMIOLOGY

This disease, like many other infections, occurs in epidemics and is spread by direct contact only rarely. Perhaps the causative organism is disseminated by carriers or diseased persons who are "moist speakers" or impolite coughers. Diseased birds have been thought to be a source of infection.[6] Coughing and sneezing animals, such as the cat, have been known to transmit the disease to man.[7] Laboratory workers after handling postmortem material have become ill with primary atypical pneumonia.[8]

As high as 50 per cent of the population of some communities have been involved, possibly because of a common viral agent.[9] The degree of severity of infection varies with the depth to which the respiratory tract is involved, from acute rhinitis and tracheobronchitis to severe pneumonia.[10] Not all persons exposed to the disease acquire it. Some having the same contacts acquire the disease in varying degrees of

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Most of the work on this paper was done while the author was a civilian.

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severity.[11] Longcope noted that persons with mild types of primary atypical pneumonia gave rise to the severer types in others, and vice versa.[12] Thus it seems that there is individual variation in susceptibility to the disease. In general, children and infants are more susceptible than adults, although the ages of higher incidence are those of young adults. No age, however, is exempt. Premature infants seem more susceptible than full term babies.[13] There is some seasonal variation: The incidence is highest during cold, damp, changeable weather. It is most common in the fall and early winter,[14] and its morbidity is not affected by the increased incidence of the common cold[15] or influenza.[16] The disease does occur in the tropics.[17]

Outbreaks often occur in crowded areas, such as schools, armies, orphanages and jails. Hospitals may be included in this list, for several reports have stated that all groups of employees in hospitals have been involved.[18] This does not exclude the physicians or the nurses, who have a high rate of incidence, perhaps because of fatigue and repeated exposure.

ETIOLOGY

Primary atypical pneumonia is a clinical entity with multiple causes. This disease may be caused by (1) a number of viruses, (2) rickettsias,[19] (3) a protozoan that produces toxoplasmosis,[20] (4) Coccidioides immitis[21] and perhaps Monilia[22] and (5) certain bacteria. Among some of the early findings that suggested a virus as cause were bacteriologically sterile cultures of blood and of postmortem material and a decreased flora in the nose, throat and sputum—especially of virulent organisms. The latter observation and also the low incidence of complications have led some workers to believe that patients with primary atypical pneumonia have an increased resistance to the pyogenic organisms.[23] Laboratory work shows many of the viruses isolated from this and similar diseases to be antigenically related. It has been thought that they may come from a parent strain.[24] Mi-

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(Footnote continued on next page)

gration of some of the parasitic merozoites through the lungs has been known to produce atypical signs and symptoms of pneumonia.[25] Again, interstitial pneumonitis has occurred in heat pyrexia.[26] Some writers have noticed on culture an increase of viridans streptococci.[27] Indeed, several cases of fatal pneumonia have been reported in which these organisms were responsible.[28] Rhoads has shown experimentally that the more fulminating attacks of primary atypical pneumonia may be due to infection by a virus and viridans streptococci.[1] Thomas and co-workers isolated a streptococcus (identified as no. 344) in 2 cases of primary atypical pneumonia which terminated fatally and showed that in 55 of 101 cases the patients had an increased titer to this organism.[29] Some pneumococci are refractory to sulfonamide compounds.[30] Gold stated that gonococci, staphylococci and pneumococci may become refractory to sulfonamide compounds if the patients are inadequately treated for as short a period as three days; moreover, the organisms remain drug fast for a year or longer.[31] Again, even though adequate treatment with sulfonamide compounds is given, some pneumococci become refractory.[32]

PREDISPOSING FACTORS

Chilling commonly predisposes to the disease.[33] Fatigue is also an important factor. Chronic diseases, such as chronic sinusitis and tonsillitis, have been thought to make the patient more susceptible. Malnutrition and lack of thiamine also seem to predispose to the disease.[34]

PRODROMAL SYMPTOMS

A dry throat or a sensation of dryness while swallowing, malaise and weakness may be noticed five to ten days before the onset of other symptoms.[35] A sensation of chilliness or a chill as well as fever may be noted a day or so before other symptoms appear. Thus a patient may have none or any one or more of these prodromal symptoms before the acute phase of the disease. There may be a cutaneous eruption early in the disease.[36]

CHIEF COMPLAINTS

A cough or a "cold" is the most common complaint.[37] Occasionally a patient calls the physician only because he has fever or because he is too weak to carry on his daily work. Other common complaints are headache, generalized muscular aches, pains in the chest, shortness of breath and abdominal pains.

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SYMPTOMS

The incubation period varies from five [38] to twenty-six [23] days. Reimann, however, expressed the opinion that in certain cases the incubation period is one or two days.[39] The average duration is fourteen to twenty-one days; more precise observations show it to be seventeen to nineteen days.[2a] The onset of the disease is usually insidious but may be acute in 25 to 33 per cent of the cases.[40] Daniels, however, reported a sudden onset in all of his cases.[41]

In infants this disease may be secondary to measles and whooping cough.[42] The onset may be that of a cold or sneezing. The children are irritable or apathetic. On the other hand, the onset can be alarming and begin with cyanosis, dyspnea and high fever. Among 74 patients reported on by Adams and his co-workers,[13c] 56 per cent of the infants with cough, dyspnea, cyanosis and high fever died; for those with a low fever the mortality rate was 20 per cent.

Cough is perhaps the most common symptom and occurs in about 85 per cent of all cases.[43] It may appear at the onset of the acute phase or during the course of the disease. Often the cough starts with a rise of temperature. It may occur in paroxysms, especially at night. Changes in the temperature of the room and the patient's moving about in bed seem to stimulate the cough.[44] It is often dry at the onset and may become productive later in the disease. The sputum is scant and may be mucoid, mucopurulent or even streaked with blood. The cough may be so severe as to cause fatigue, excess sweating and muscular aches in the abdomen and chest. A burning sensation in the chest may be due to severe tracheitis or tracheobronchitis. Other pains in the chest that should be mentioned are those due to pleurisy and broken ribs, both of which occur rarely.

Headaches are commonly frontal or periorbital or affect the entire head. They are sometimes described as throbbing. Often these headaches are so severe that they do not respond to ordinary treatment. Not infrequently there is a burning sensation in the eyes. Lacrimation occurs only occasionally. Pain on rotation of the eyeballs, such as occurs in influenza, is rare and is though to be of aid in the differential diagnoses [45]; yet soreness of the eyes on motion does occur not uncommonly.[46] "Tiredness of the eyes" seems to be a part of the generalized weakness and the generalized muscular ache that are so commonly present. Accompanying the lack of strength there may be sweating; in the more severe forms the sweat is drenching. Frank chills are occasionally encountered, but most patients experience only a sensation of chilliness—often alternate chilliness and fever.

Dyspnea and cyanosis may occur on the fourth and fifth days of the disease.[23] These symptoms may be evidence of bronchiolar and alveolar occlusion, atelectasis, a hyalin-like lining of the alveoli, edema and infiltration of the interalveolar tissue and possibly enlarged hilar lymph nodes. Other respiratory symptoms are rhinitis, pharyngitis and sometimes hoarseness and aphonia.[47] The two last-mentioned symptoms may precede the onset of the disease and disappear a few days after the beginning of the illness. Other symptoms may be anorexia and occasionally vomiting, abdominal distention, constipation and diarrhea. Often return of appetite is the first sign of improvement.

The fever is usually of low grade, although the temperature may be as high as 105 or 106 F. Some patients may be entirely afebrile; this has been noted in infants [13a] as well as in adults.[48] The fever curve may be biphasic [49]; i. e., there may be fever for one or several days (even up to

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47. Reimann.[11b] Reimann and Havens.[18c]

48. Drew, Samuel and Ball.[19a] Dingle and others.[2a] Lyght and Cole.[37]

49. (*a*) Lusk and Lewis.[2b] (*b*) Adams.[13a] (*c*) Schmitz, R. C.: Primary Atypical Pneumonia, Wisconsin M. J. **43**:228 (Feb.) 1944.

seven days [50]), and then the temperature may return to normal, with some remission of symptoms for a day or so, only to rise again with exacerbation of symptoms. The fever has a typical swinging character; i. e., the temperature is usually lower in the morning and higher in the afternoon or vice versa. Defervescence is usually by lysis but occasionally by crisis.[51] The fever, depending on the severity of the disease, may last from two [15b] to forty-three [52] days or even longer.

The heart rate is not increased in proportion to the rise in temperature as a rule. There may be bradycardia, or in more severe forms this slow rate may give way to a more rapid one during convalescence. Tachycardia may be present at the onset. Owen stated that a rise in pulse rate suggests an increasing pulmonary lesion and that a slow pulse, despite high fever, is little cause for concern.[5] The respiratory rate, as a rule, is only slightly increased. Herpes labialis and epistaxis are rare [53]; however, Cutts reported that 23.4 per cent of his 60 patients had herpes labialis.[54] Loss of weight and relapses are not uncommon. Berryhill and associates stated that 7 patients had recurrences within two years.[14e] Dochez stated that 1 patient had as many as four relapses.[55] Thus it would seem that as yet little can be said about immunity to this disease.

The amount of discomfort and the disposition of the patients vary. Malaise in the milder form of the disease may not be severe. Green reported the case of a soldier who while he had a temperature of 105 F. was seen sitting up in bed, smoking and reading a comic strip.[3a] It is obvious at once that such persons, who do not feel ill, are up and about doing their daily work for weeks and even months before they consult a physician. This is especially true if they are completely or nearly asymptomatic [56]; in this event they seldom seek medical aid. It is this group that is thought to be responsible for the spread of the disease.[15e]

PHYSICAL CHARACTERISTICS

The nasal mucosa is often hyperemic, and the pharynx may be injected. The throat does not have the generalized edema seen in colds.[57] In general, the physical manifestations in the chest are surprisingly few. In about 50 per cent of Green's 110 cases no abnormalities of the chest were found on the patients' admission to the hospital.[3a] Dingle and co-workers could find no abnormal signs at any time in a few cases despite the fact that the location of the lesion was known.[22] Decreased breath sounds are more frequent than bronchial breathing. One may hear only fine or medium, moist rales in late inspiration. Often these rales do not appear until the temperature has fallen.[58] In 57.2 per cent of 155 cases the first signs were presented within three days, in 27 per cent in four to seven days, in 5.5 per cent in seven to nine days and in 3.1 per cent in ten or more days.[15b] Duggan reported that he had heard the initial rales in some of his cases as late as the eleventh day.[40b] These may exist for several weeks after the patient has apparently recovered [59] and the roentgen plate cleared. At times rhonchi may be heard, especially during the later stages. In the more severe forms consolidation may be noted. Abdominal tenderness and rebound tenderness may be elicited. Occasionally the spleen and the liver are palpable.

PATHOLOGIC CHARACTERISTICS

Grossly the lung is crepitant, with isolated areas of pink or gray consolidation that vary in size.[60] There may be hemorrhagic areas in the lungs.[61] Necrosis and ulceration of the epithelium may be found in the bronchi and bronchioles, with resulting cellular debris filling the lumens.[18a] Often a thick exudate of mucus, desquamated cells, monocytes and a few neutrophils and eosinophils fills the small bronchi, bronchioles and alveoli. Beyond the obstruction there is atelectasis; in the other parts of the lung there may be emphysema. The blood vessels may be thrombosed [28b] and necrotic and show periarteritic changes.[27b] An infarct in a lung has been reported.[14b] Spread of the pulmonary lesion is not via the lumen of the respiratory tree but

50. Herxheimer, H. G. J., and McMillan, A. J.: Atypical "Influenzal Pneumonia" at a School, Brit. M. J. **2**:513 (Oct. 31) 1942.

51. Dingle and others.[2a] Lyght and Cole.[37]

52. (*a*) Reimann.[11b] (*b*) Shone, S., and Passmore, R.: Pneumonitis Associated with Autohemagglutination, Lancet **2**:445 (Oct. 9) 1943.

53. Needles, R. J., and Gilbert, P. D.: Primary Atypical Pneumonia: Report of One Hundred and Twenty-Five Cases, with Autopsy Observations in One Fatal Case, Arch. Int. Med. **73**:113 (Feb.) 1944.

54. Cutts, F. B., and Lawson, H. A.: Primary Atypical Pneumonia, Etiology Unknown, Rhode Island M. J. **27**:11 (Jan.) 1944.

55. Dochez, A. R., in discussion on Reimann, Havens and Price.[24f]

56. Owen.[5] Gallagher.[14c] Andrus, P. M.: Silent Bronchopneumonia, Canad. M. A. J. **47**:339 (Oct.) 1942. Fredd, H.: Atypical Pneumonias, New York State J. Med. **41**:34 (Jan. 1) 1941. Ramsey, H., and Scadding, J. G.: Benign Bronchopulmonary Inflammations Associated with Transient Radiographic Shadows, Quart. J. Med. **8**:79 (April) 1939.

57. Primary Atypical Pneumonia, Etiology Unknown, Army M. Bull., April 1942, no. 61, p. 31.

58. Dingle and others.[22] Miller, F. N., and Hayes, M. G.: Bronchopneumonia of Mild Severity at University of Oregon, Northwest Med. **38**:12 (Jan.) 1939.

59. Longcope.[14b] Shone and Passmore.[52b]

60. Kneeland and Smetana.[27b] Needles and Gilbert.[53]

61. Adams.[18a] Longcope.[14b] Schmitz.[49c]

rather by the interstitial tissue of the alveoli adjacent to the bronchioles.[62] Bronchoscopy reveals a mucosa that is inflamed and congested and that bleeds readily, as compared with the moderately inflamed mucosa characteristic of pneumococcic pneumonia.[22]

Microscopically one may see areas of hemorrhage in the lungs. The interalveolar tissue is edematous, thickened and infiltrated primarily by monocytes.[27b] The alveoli in addition may have a hyalin-like lining.[63] Metaplasia of the alveoli has been seen.[18d] Inclusion bodies have been found in the epithelial cells of the respiratory tract.[64] Adams reported that these bodies are found with increasing difficulty if the course of the disease has extended beyond several days or if a secondary infection has set in.[13a] Gedgoud, however, reported the finding of inclusion bodies in a child who died of the disease after twenty-three days of illness. He also stated that he found these bodies in 25 of 35 women from whom he had taken vaginal and throat smears.[64d] Inclusion bodies are not specific for viral infection, for they may be due to Haemophilus pertussis, Pasteurella tularense, toxins, irritative chemicals.[24f] or the protozoan of toxoplasmosis.[65] Other pathologic changes noted have been hemorrhage of the adrenal glands,[13a] acute splenic tumor,[11a] focal necrosis of the liver,[27b] acute follicular splenitis, necrosis of enlarged malpighian corpuscles of the spleen, edema of the meninges, mesenteric lymphadenitis [22] and hyaline necrosis of the diaphragmatic muscle.[5]

LABORATORY FINDINGS

In general, during the early stages of primary atypical pneumonia there is a normal, slightly depressed white cell count or even a slightly increased count.[66] Cass, however, reported counts as low as 2,500 to 1,800.[44] He stated that those patients who have extremely low blood counts are severely ill; thus he concluded that the more severe the leukopenia in the early stages the worse the prognosis. Likewise any sharp rise of the number of white cells from leukopenia to marked leukocytosis may be indicative of bad prognosis. McKinlay stated that so long as the original leukopenia is retained during the acute phase of the disease and is accompanied by consistently negative bacteriologic findings the prognosis is good.[67] An initial leukocyte count of 12,000 or higher was found to be due to "walking pneumonia," previous vomiting and secondary infection of the sinuses, ears, pharynx, etc.[14a]

During convalescence it is common to have a leukocyte count of 10,000 to 15,000. The count may go as high as 20,000 [68] or 22,000 [69] and may be erroneously thought to be indicative of a secondary infection, but this is not the rule. Lyght and Cole pointed out that a rise in the white cell count, if it does not go too high, is usually a good sign.[37] The differential count reveals that the polymorphic neutrophils range between 65 and 90 per cent of the total count. According to Drye, lymphocytosis with 50 per cent lymphocytes is not uncommon. He also noted that the total white cell count began to rise the second or third day before the temperature fell and finally reached a peak two or three days after the temperature became normal.[79] In the series of infants at the University of Minnesota Hospital the average leukocyte count in 1937 was 19,140 with 48 per cent neutrophils, and in 1940 it was 13,500 with 47 polymorphic neutrophils.[13b] Toxic granules may be seen in the cells, and there is usually a shift to the left. A differential count of 26 per cent eosinophils,[71] 16 and 25 per cent monocytes [72] and a few granulocytes has been encountered.[71] Reimann found stippled erythrocytes and Döhle bodies in neutrophils.[11b]

Other laboratory findings are: increase of pressure of the cerebrospinal fluid to 250 mm. of water,[73] increase in the number of spinal fluid

62. (*a*) Green and Eldridge.[3a] (*b*) Saphir, O.: Pathological Changes in So-Called Atypical Pneumonia, Radiology **40**:339 (April) 1943. (*c*) Boyd, W.: The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1940, p. 159.

63. Reimann, Havens and Price.[24f] Kneeland and Smetana.[27b] Saphir.[62b]

64. (*a*) Adams.[13a] (*b*) McCordock and Smith.[42a] (*c*) Schmitz.[49c] (*d*) Gedgoud, J. L.: The Diagnosis of Virus Pneumonitis in Infancy, Nebraska M. J. **28**: 51 (Feb.) 1943.

65. Sabin, A. B.: Toxoplasmic Encephalitis in Children, J. A. M. A. **116**:801 (March 3) 1941.

66. Peterson, O. L., and Finland, M.: Modern Treatment of Pneumonia, M. Clin. North America **27**:1291 (Sept.) 1943.

67. McKinlay, C. A., and Cowan, D. W.: Acute Respiratory Infections Including Lobar Pneumonia and Atypical Pneumonia in a Young Adult Group, Journal-Lancet **61**:125 (April) 1941.

68. (*a*) Murray.[14a] (*b*) Langille, J. A.: Acute Pneumonitis or Virus Pneumonia, Nova Scotia M. Bull. **21**:333 (Nov.) 1942.

69. Smiley, Showacre, Lee and Ferris.[14d] Solomon and Kalkstein.[28a] McKinlay and Cowan.[67] Langille.[68b]

70. Drye, J. C., in discussion on Flexner and Garson.[125f]

71. Contratto, A. W.: So-Called "Atypical Pneumonia" Among College Students, New England J. Med. **229**:229 (Aug. 5) 1943.

72. (*a*) Shone and Passmore.[52b] (*b*) Collen, G. W.: Virus Pneumonia, Permanente Found. M. Bull. **1**:45 (Oct.) 1943. (*c*) Young, L. E.; Storey M., and Redmond, A. J.: Clinical and Epidemiological Features of an Outbreak of Primary Atypical Pneumonia of Unknown Etiology Among Hospital and Medical School Personnel, Am. J. M. Sc. **206**:756 (Dec.) 1943.

(Footnotes continued on next page)

cells [74] to 2,000 cells per cubic millimeter, 90 per cent of which are neutrophils, increase of cerebrospinal fluid protein [75] content and lowering of the blood serum albumin-globulin ratio.[27b] The sedimentation rate is increased, especially toward the end of the disease. Van Ravenswaay and associates showed that for patients who are kept in bed until the sedimentation rate is 10 mm. in one-half hour recurrences are fewer and the total time in bed per patient is less.[40d] Helwig and Freis showed that the sedimentation rate in 1 case was increased but that this did not occur when the citrated blood was kept at body temperature.[76] In primary atypical pneumonia there is no hypoaminoacidemia, excess retention of sodium chloride and water in the acute stage or excess excretion of sodium chloride and water during convalescence, as in pneumococcic pneumonia.[77]

Cold agglutinins appear during the acute stage (after the eighth to tenth day) of the disease,[78] and the height of the titer has no relationship to the severity of the disease or to the size of the pulmonary lesion. In a group of cases in Great Britain during the winter of 1942-1943 these agglutinins occurred in more than 90 per cent of the cases.[78d] Difficulties in making the major cross matches as well as agglutination of cells in the red cell pipet due to cold agglutinins of these patients may be overcome by working with solutions and instruments at 37 C.[79] The urine is usually cloudy, has a few white cells in it occasionally and has a slight trace of albumin, as one would expect in toxic, febrile diseases. Glycosuria that cleared immediately has been reported.[5] The serologic reactions have been reported as shifting [80] and as positive.[81] Langille had a case in which the Kahn test gave a positive but the Eagle test a negative reaction; the serologic reaction became completely negative in two months.[68b] A gold salt curve has been reported as 1122210000.[33] The serum in several cases gave a positive reaction to a Weil-Felix agglutination test.[82] The Frei test has been reported to give positive results in some cases.[24h] Agglutination of sheep cells has been reported in cases with negative serum reactions previously.[83] Electrocardiographic changes according to Kurtz are low voltage, deviation of the ST segments, flattening of the T waves, severe sinus arrhythmia, bradycardia and conduction disturbances. Deviation of the axis to the left has also been noted. Sinus arrhythmia and bradycardia may exist for several weeks or a few months after recovery; during this time the patient has a feeling of malaise.[84] One must rule out, electrocardiographically, coronary occlusion.[85]

ROENTGEN FINDINGS

Roentgenographic evidence appears about one [14a] to four [86] days after the onset of the disease. As early as 1934 Gallagher noted that roentgenograms show more than the physical changes would seem to justify.[87] This may be due to interstitial involvement of the lungs and possible lack of consolidation within the alveoli, or the area of consolidation or the involved alveoli may be sandwiched deeply between essentially normal pulmonary tissue. On the other hand, the patient may be extremely ill with the disease although the roentgen findings may be minimal or even absent.[88] In mild forms the roentgenogram may show only an increased

73. (*a*) Green and Eldridge.[38a] (*b*) Reimann.[11b] (*c*) Sheppe, W. M.; Osterman, A. L.; Ahroon, C. R., and Zuflacht, J. J.: Meningomyelitis: A Complication of Primary Atypical Pneumonia, J. A. M. A. **122**:1245 (Aug. 28) 1943.

74. (*a*) Green and Eldridge.[38a] (*b*) Reimann.[11b] (*c*) Sheppe, Osterman, Ahroon and Zuflacht.[73c] (*d*) Campbell, T. A.; Strong, P. S.; Grier, G. S., and Lutz, R. J.: Primary Atypical Pneumonia: A Report of Two Hundred Cases at Fort Eustis, Virginia, J. A. M. A. **122**:723 (July 10) 1943.

75. Owen.[5] Campbell, Strong, Grier and Lutz.[74d]

76. Helwig, F. C., and Freis, E. D.: Cold Autohemagglutinins Following Atypical Pneumonia Producing the Clinical Picture of Acrocyanosis, J. A. M. A. **123**:626 (Nov. 6) 1943.

77. Emerson, K., Jr.; Curnen, E. C.; Mirick, G. S., and Ziegler, J. E.: Chloride Metabolism and Plasma Amino Acid Levels in Primary Atypical Pneumonia, J. Clin. Investigation **22**:695 (Sept.) 1943.

78. (*a*) Peterson and Finland.[66] (*b*) Horstmann, D. M., and Tatlock, H.: Cold Agglutinins: A Diagnostic Aid in Certain Types of Primary Atypical Pneumonia, J. A. M. A. **122**:369 (June 5) 1943. (*c*) Turner, J. C.: Development of Cold Agglutinins in Atypical Pneumonia, Nature, London **151**:419 (April 10) 1943. (*d*) Turner, J. C., and Jackson, E. B.: Serological Specificity of an Auto-Antibody in Atypical Pneumonia, Brit. J. Exper. Path. **24**:121 (June) 1943.

79. Dameshek, W.: Cold Agglutinins in Acute Hemolytic Reactions in Association with Sulfonamide Medication and Infection, J. A. M. A. **123**:77 (Sept. 11) 1943.

80. Owen.[5] Kneeland and Smetana.[27b]

81. Green.[38a] Owen.[5]

82. (*a*) McNaught, J. B.: Virus Pneumonia: A Review of the Pathology, California & West. Med. **59**:220 (Oct.) 1943. (*b*) Sachs, J.: Recent Advances in Diagnosis and Treatment of Virus and Atypical Pneumonia, New York State J. Med. **44**:485 (March 1) 1944.

83. Shone and Passmore.[52b] Young, Storey and Redmond.[72e]

84. Kurtz, C. M.: Personal communication to the author. This work is to be published at a later date.

85. Fuller, C. C., and Quinlan, J. W.: Acute Pneumonitis and Pericarditis, New England J. Med. **229**: 399 (Sept. 2) 1943.

86. McCarthy, P. V.: Primary Atypical Pneumonia of Unknown Etiology, Radiology **40**:344 (April) 1943.

87. Gallagher, J. R.: Bronchopneumonia in Adolescence, Yale J. Biol. & Med. **7**:23 (Oct.) 1934.

88. Berryhill, Hedgpeth, Morgan, Stone and Smith.[14a] Cass.[44] Schmitz.[49c] Levin, S. L.: Primary Atypical

density in the costophrenic angle [89] or at the cardiophrenic angle.[19a] Likewise there may be just a diffuse increased density of one lobe. One may notice only an increase in the pulmonic markings, resembling bronchitis. This is due to peribronchial and perivascular infiltration. The spread is via continuity and contiguity of tissue, and this process is responsible for the interbronchial cottony shadows. The lesions are usually found in the lower lobes. An entire lobe may be involved, in all probability because of the extension and coalescence of the cottony areas. The plate may resemble that seen in lobar pneumonia except that the shadow does not obscure the vascular or osseous markings.[8a] There may at times be visceral pleural thickening that may also resemble lobar pneumonia.[90] Inadequately treated pneumococcic pneumonia may show reticular markings that will not clear as rapidly as those seen in primary atypical pneumonia.[19a] In other cases there may be a fan-shaped lesion in the hilus or less commonly in the periphery of the lung, or a lesion that spreads into one or both lungs. Patients with diffuse patchy involvement generally have a more prolonged course than those with a localized lesion.[57] The clearing time may range from three [22] to more than sixty-two days.[91] McCarthy suggested that patients be dismissed from the hospital only after the roentgenogram is relatively normal.[86]

The extent of involvement of the parenchymal tissue is not always apparent. There may be continual changes for some days or weeks, such as extension or clearing. This mutation is of diagnostic value, especially in differentiating this disease from tuberculosis; thus differential diagnosis requires serial plates. At the Middlesex County Sanatorium plates are taken at intervals of two weeks before the diagnosis of tuberculosis is made.[92] Formation of pseudocavities in this pulmonary condition is also differentiated from tuberculosis by consecutive plates.[19a] Thus serial roentgenograms should be taken for draftees before they are rejected because of possible tuberculosis. The hilar nodes are not so enlarged in early tuberculosis, and the striations extending to the hilus from the consolidated tuberculous areas are more extensive than in primary atypical pneumonia.[19a] There is little tendency in this disease to involve the pleura.[22] Bowen stated that at times there are residual fibrosis and incomplete reabsorption of the pulmonary lesion; this makes the differential diagnosis from tuberculosis even more difficult.[93] Thus roentgenologically primary atypical pneumonia must be differentiated from acute bronchitis, bronchopneumonia, cancer, early pulmonary abscess, tuberculosis, pneumococcic pneumonia and acute bronchiectasis.[11a]

DIAGNOSIS

Diagnosis can be made by (1) the roentgenograms, (2) the history, and the physical examination and (3) the therapeutic test with sulfonamide compounds and the processes of elimination, which are the least desirable methods of diagnosis. The results may be misleading in persons with inadequately treated or sulfonamide-resistant coccic pneumonia. This is particularly true of children with pneumonia.[94]

The isolation of cold agglutinins (autohemagglutinins) is now suggested as an aid in diagnosis of certain types of primary atypical pneumonia.[95]

DIFFERENTIAL DIAGNOSIS

Influenza is the most difficult condition to differentiate from the mild form and the early stages of this disease. The roentgenogram in influenza is not abnormal.[19a] The marked inflammatory reaction in the pharynx [96] and the catarrhal symptoms of influenza [97] are absent in primary atypical pneumonia. Pain on rotation of the eyes as elicited in influenza is rarely present,[45] but aching of the eyes is not uncommon. The tenderness of the bones and the gastrocnemius muscle that may occur in influenza was not present in Longcope's cases.[14b] The symptom of generalized muscular aches is more distressing in influenza, and the headache as atypical pneumonia progresses seems to be more disturbing.[97] In

Pneumonia, Etiology Unknown: Report of Thirty-Five Cases, M. Bull. Vet. Admin. **20**:122 (Oct.) 1943.

89. (*a*) Murray.[14a] (*b*) Duggan and Powers.[40b] (*c*) Scott, W. G., and Jones, H. L., Jr.: Acute Pneumonitis, Am. J. Roentgenol. **50**:444 (Oct.) 1943.

90. Curtzwiler, F. C., and Moore, B. E.: Primary Atypical Pneumonia of Unknown Etiology, Radiology **40**:347 (April) 1943.

91. Haight, W. L., and Trolinger, J. H.: Primary Atypical Pneumonia, Etiology Unknown, U. S. Nav. M. Bull. **41**:988 (July) 1943.

92. Davenport, L. F.: Atypical Pneumonias, Bull. New England M. Center **4**:17 (Feb.) 1942.

93. Bowen, A.: Acute Influenza Pneumonitis, Am. J. Roentgenol. **34**:168 (Aug.) 1935.

94. Finland, M.: The Diagnosis of Virus and Bacterial Pneumonia in Children, New England J. Med. **229**:199 (July 29) 1943.

95. (*a*) Horstmann and Tatlock.[78b] (*b*) Peterson, O. L.; Ham, T. H., and Finland, M.: Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonia, Science **97**:167 (Feb. 12) 1943. (*c*) Turner, J. C.; Nisnewitz, S.; Jackson, E. B., and Berney, R.: Relation of Cold Agglutinins to Atypical Pneumonia, Lancet **1**:765 (June 19) 1943. (*d*) Meiklejohn, G.: The Cold Agglutination Test in the Diagnosis of Primary Atypical Pneumonia, Proc. Soc. Exper. Biol. & Med. **54**:181 (Nov.) 1943.

96. Opie, E. L.: The Pathologic Anatomy of Influenza, Arch. Path. **5**:285 (Feb.) 1928.

97. Field, H.: Acute Respiratory Infections, Including Virus Pneumonia, West Virginia M. J. **40**:69 (March) 1944.

influenzal pneumonia there are early extreme (grayish) cyanosis [98] and dyspnea, increased respiratory rate, prostration and euphoria. This type of pneumonia is said to occur only during epidemics of influenza.[62c]

Bronchopneumonia usually gives little trouble in the differential diagnosis. To the aged, in whom the onset of pneumonia is insidious and the fever and white cell count are low, sulfonamide compounds are justifiably given until one is certain that the patients have primary atypical pneumonia. Patients with bronchitis who have no history of allergy, previous colds or influenza should be examined carefully for possible primary atypical pneumonia.[57] The hyperemia and generalized edema of the throat seen in the common cold are not present [57]; however, hypertrophy of lymphoid follicles on the posterior pharyngeal wall is occasionally seen.[46] Atypical pneumonia, like the lobar type, has been confused with acute appendicitis, and under such conditions appendixes have been removed.

Pneumococcic pneumonia does not produce a rise in the titer of cold agglutinins during the second and third weeks. Likewise, there is usually no significant change in the titer of cold agglutinins in advanced tuberculosis, during convalescence from sinusitis, in hemolytic streptococcic sore throat, or in the common cold. Rarely does the titer in a normal person exceed 1 : 16.[95c]

The differential diagnosis includes lobar pneumonia, influenza, psittacosis, tuberculosis, bronchitis, bronchopneumonia, bronchiectasis, malaria, typhoid, undulant fever, tularemia, fungous diseases of the lungs, toxoplasmosis and pneumonia produced by measles, influenza, chickenpox, vaccina and variola.

COMPLICATIONS

Although complications are uncommon, they are mentioned here in order that a fuller understanding of the disease may be had.

Kneeland and Smetana reported on a patient who had slightly elevated erythematous areas of skin that ranged up to almost 2 cm. in diameter. This eruption occurred early, was generalized and was accompanied by a relapsing fever. The patient was stuporous; he had a stiff neck and a positive Babinski reaction on the left side. Another of their patients had severe polyarthritis with heat and swelling that did not respond to salicylates. There were also pericarditis and bilateral pleural effusion. This patient required four months of hospitalization and had a prolonged convalescence. Other complications were orthopnea, heart failure, urticaria, thrombophlebitis, oliguria, gross hematuria, hypoproteinemia, meningism, coma and jaundice.[27b] Longcope reported bilateral thrombi in the legs with pulmonary infarcts [14b] and also occasional erythematous areas on the skin.[18d] Allen reported otitis media, urticaria, acute maxillary sinusitis, peritonsillar abscess and even necrosis of the cervical nodes as complications.[99] Reimann added a few cases of encephalitis and such signs and symptoms as positive Kernig's sign, ankle clonus, mental confusion and euphoria.[11b] Cass and a number of others [100] have reported cases in which empyema occurred. Adams had a case of secondary infection of the lungs with a pneumococcus and another case of pulmonary abscesses.[13a] McKinlay found on postmortem examination fresh cardiac lesions that were thought to have occurred during the course of primary atypical pneumonia. The valvular damage simulated the lesions of rheumatic fever.[36b] Longcope [12] and Moore and his associates [98] reported deaths from this disease of patients who had had rheumatic endocarditis. Green reported dilatation of the heart, which regressed as the patient improved.[8a] Other complications reported are: ulceration of the soft palate; tonsillitis; streptococcic pharyngitis [14a]; erythema multiforme [101] with involvement of the mucous membrane; staphylococcic pneumonia; asthmatic breathing [102]; a continued productive cough suggesting bronchiectasis [103]; massive hemoptysis [104]; chronic pyelonephritis; acute focal hepatitis [24f]; acute hemolytic anemia [105]; pleurisy; spontaneous pneumothorax; eustachian pyosalpingitis; toxic myocarditis; acute cystitis, nephritis and infectious mononucleosis [37]; conjunctivitis and stomatitis [106]; nonspecific urethritis [40d]; meningomyelitis [73e]; facial palsy [5]; myelitis with resulting paralysis of the legs, and fractured ribs due to excessive strenuous coughing.[74d] There may also be a late manifestation of acrocyanosis.[76] Relighting of old tuberculous lesions has occurred.[107] The bronchi may dilate, producing pseudobronchiectasis; they return to normal in about three months.[108] Thus one must evaluate the immedi-

98. Moore, G. B.; Tannenbaum, A. J., and Smaha, T. G.: Atypical Pneumonia in an Army Camp, War Med. **2**:615 (July) 1942.

99. Allen, W. H.: Acute Pneumonitis, Ann. Int. Med. **10**:441 (Oct.) 1936.

100. Adams.[13a] Murray.[14a]

101. Markham, J.: Acute Pneumonitis: An Atypical Bronchopneumonia of Virus Origin, Canad. M. A. J. **47**:133 (Aug.) 1942.

102. Longcope.[14b] Kneeland and Smetana.[27b]

103. Dingle and Finland.[11a] Van Ravenswaay and others.[40d]

104. Owen.[5] Van Ravenswaay and others.[40d]

105. Horstmann and Tatlock.[78b] Dameshek.[79]

106. Van Ravenswaay and others.[40d] Contratto.[73]

107. Maxfield, J. R., Jr.: Atypical Pneumonia with Leukopenia, Texas State J. Med. **35**:340 (Sept.) 1939.

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ate history of men with bronchiectasis who are to be rejected by or discharged from the armed forces.

TREATMENT

Harris and Stokes were able to reduce the incidence of infections of the upper respiratory tract in a pediatric ward with the use of vaporized propylene glycol.[109] Although this aerosol does not destroy organisms afloat on particles of dust, it does destroy germs ejected into the air with a fine spray of moisture.[110] Perhaps this material could be used to prevent the spread of this and other diseases in Army camps, schools, theaters, hospital wards, etc. The vapor is nonexplosive if kept at the concentrations required to sterilize air.[111] Triethylene glycol is thought to be superior to propylene glycol.[112]

Despite isolation the disease has been known to spread.[6b] Oxygen is indicated for patients with delirium, cyanosis, dyspnea and hyperpnea. Epinephrine, ephedrine and helium and oxygen under pressure have been used for asthmatic breathing.[113] In cases of pulmonary collapse bronchoscopy is recommended.[114] Steam inhalation and codeine are used for the dry cough. Expectorants and benzoin inhalants have been used but Cass has stated that they may aggravate the cough.[44] Longcope stated that the cough in severe cases is often refractory to codeine, and he recommended oxygen for its control.[18d] Codeine and ice caps are used for headaches. Lumbar puncture has been performed for relief of severe headaches.[2a] Because of marked sweating, diaphoretics such as salicylates, aminopyrine and acetophenetidin are to be avoided.[18c] On the other hand, when a patient has a high temperature and is not perspiring, the diaphoretics may be comforting.[44] They are indicated for generalized muscular aches, including backache. A tight binder has been recommended for abdominal muscular pain.[18c] Fluids are usually forced. In the event of excessive sweating a 3 per cent solution of sodium chloride and cortin has been given to replace the lost salt.[98] Transfusions are indicated for secondary anemia and plasma for hypoproteinemia.

The treatment of infants is essentially the same as that of adults. The liberal use of fluids, however, is to be avoided, for they are poorly tolerated and seem to aggravate the dyspnea, cyanosis and cough.[18c] Postural drainage may be indicated with aspiration of the mucus from the nose and throat. Thiamine hydrochloride and nicotinic acid have been used for treatment and prevention of delirium.[115]

In general, most authorities agree that sulfonamide compounds are not indicated in treatment of this disease unless there is definite evidence that secondary infection is present or that such a complication may set in. It may be stated that sulfonamide drugs given prior to the time the temperature drops in its biphasic curve may produce a false impression of a favorable response and thus seemingly justify continued drug therapy.[116] When the diagnosis is not definite it would seem justifiable to use the drugs, but only for forty-eight to seventy-two hours if there is no response. Some workers have stated that while chemotherapy was being employed the patients' temperatures were occasionally reduced.[117] Shone used sulfapyridine with a resultant reduction in the temperature, and when administration of the drug was stopped, the patients had exacerbation of fever.[52b] This confirms the work of Beeson, who showed that sulfapyridine is an antipyretic.[118] Markham stated that sulfonamide drugs have no effect on the patients' temperatures, and that if their administration is stopped, the patients are spared nausea and malaise.[101] In addition, some of these drugs when given in full doses for a period may produce sensitivity to the drugs, acute hemolytic anemia[119] or some other types of anemias, agranulocytosis, increased leukocytosis,[120] cold

108. Blades, B., and Dugan, D. J.: Pseudo-Bronchiectasis Following Atypical Pneumonia, Bull. U. S. Army M. Dept., November 1943, no. 70, p. 60.

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agglutinins[79] and anorexia. There is no therapeutic response, and the patients often state that they feel better after administration of the drug is stopped. Moreover, these drugs may reduce aviators' ceiling zero[89c] as well as impair judgment.[121] Cold agglutinins plus sulfonamide drugs may be responsible for acute hemolytic anemia.[79] Furthermore, Royster expressed the opinion that chemotherapy prolongs the disease and seems to make patients worse.[122] Suttenfield stated the view that withdrawal of the sulfonamide drugs definitely saved several patients' lives.[17b] Treatment with sulfonamide drugs alone has resulted in a mortality rate of 0.2 per cent.[123] Penicillin has been unsatisfactory in the treatment of this disease.[124]

Transfusions of whole blood have been given with the specific hope of imparting immune bodies to patients. Adams and co-workers reported administration of 30 cc. of normal adult blood to 7 babies early in the course of the disease and to 7 others before they had become ill. No deaths occurred in this group of 14 infants.[13c] Flexner used convalescent whole blood with good results, as others have done.[125] On the other hand, Young gave plasma and whole blood from convalescent donors to 12 patients without any definite response.[72c] Immune bodies have been proved to exist in the blood of convalescent patients.[126] The titer of the antibodies during convalescence is greater than that during the acute phase.[6e] Roentgen ray treatment has been said to abate the cough, bring the temperature down within forty-eight[127] to seventy-two hours and clear the roentgenogram.[128] Naval officers stated that they felt they had reduced the febrile period, the number of days of resolution and the total number of days of illness, roughly speaking, by one half through roentgen ray treatment.[15b]

PROGNOSIS

Prognosis in general for the majority of cases is good. This disease in its severe form, superimposed on an already damaged heart, will warrant a guarded prognosis. A number of deaths have been reported in the United States.[129] Undoubtedly reports of some cases that terminated fatally have not appeared in the literature. In 1,862 cases that occurred in an army camp a mortality rate of 0.26 per cent was reported.[40d] Among civilians the rate is estimated to be 2.4 per cent.[5]

CONCLUSIONS

Treatment is symptomatic. Sulfonamide drugs may be detrimental, and penicillin seems to be without results. The administration of oxygen under positive pressure in severe pneumonia may be life saving. With the use of roentgen rays and convalescent serum and with the sedimentation rate as a guide to the time of dismissal, the period of hospitalization may be reduced.

In rejecting persons for the armed forces and in discharging military personnel because of tuberculosis or bronchiectasis, one must consider the possibility of recent primary atypical pneumonia.

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EFFECTS OF COLD AIR ON THE AIR PASSAGES AND LUNGS

AN EXPERIMENTAL INVESTIGATION

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BOSTON

The absence of reliable information concerning the effects of cold air on the air passages and the lungs and concerning the rate at which inhaled cold air is warmed within the body led to the undertaking of this investigation on dogs.

In order to observe the pathologic and physiologic changes resulting from the inhalation of cold air independent of any indirect or secondary effects that might result from the simultaneous chilling of the surface of the body, the air was brought into the mouth and throat through a vacuum-jacketed (Dewar) cannula, and the animals were not otherwise exposed to cold. Care was exercised to see that the dogs had no source of air for respiration other than that which had passed through a cooling system.

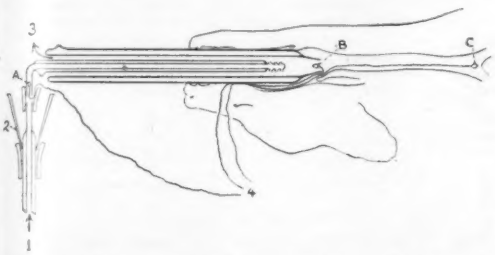

Fig. 1.—Diagrammatic representation of the cannula through which cold air was brought to the larynx; *1*, source of cold air which had been chilled by circulation through a bath of liquid nitrogen and alcohol; *2*, glass flange filled with liquid nitrogen to prevent warming of the noninsulated segment of the conduction system; *3*, outer compartment of the transoral cannula through which exhaled air was discharged; *4*, thermocouple leads to the potentiometer and to the galvanometer; *A*, thermocouple in the cold air stream before entering the inner compartment of the cannula; *B*, thermocouple in the laryngeal opening of the cannula; *C*, thermocouple at the bifurcation of the trachea.

The air was chilled by passage through a radiator (converted automobile heater) which was immersed in a large Dewar container filled with a mixture of liquid nitrogen and alcohol. The rate of flow was maintained at 30 liters per minute by means of a flowmeter interposed between the compressed air line and the cooling mixture. To prevent blockade of the cooling system by formation of ice it was necessary to pass the air through a trap before it entered the radiator. This trap, which was immersed in the nitrogen-alcohol mixture, consisted of a tube 25 cm. long and 2 cm. in diameter. After leaving the flowmeter and before entering the radiator the air passed through this tube, where the moisture contained by it was condensed and frozen.

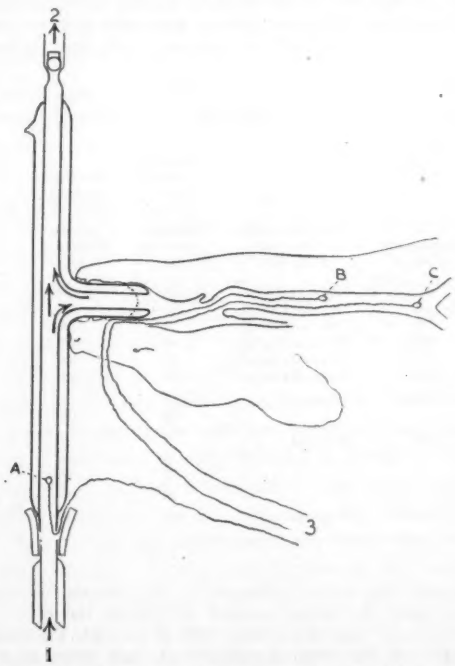

Fig. 2.—Diagrammatic representation of the cannula through which cold air was brought to the midportion of the mouth: *1*, source of cold air which had been chilled by circulation through a bath of liquid nitrogen and alcohol; *2*, outlet for exhaled air; *3*, thermocouple leads to the potentiometer and to the galvanometer; *A*, thermocouple in the cold air stream before entering the cannula; *B*, thermocouple in the midportion of the trachea; *C*, thermocouple at the bifurcation of the trachea.

After leaving the radiator the air was conducted through a vacuum-jacketed tube to the animal's mouth. In one series of animals the cold air was conveyed directly to the laryngeal orifice (fig. 1), and in another series it was conveyed to a point about midway between the front teeth and the larynx (fig. 2). In each instance the transoral cannula was constructed on the

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Dr. F. C. Henriques Jr. aided in adaptation and calibration of the recording instruments used in this investigation.

Dewar principle in order to reduce to a minimum the conduction of heat through its wall.

The laryngeal cannula (fig. 1) used in the first series of animals was constructed in such a way that the cold air was brought through an inner compartment to the laryngeal orifice for inhalation and was exhaled through an outer compartment. The inhalation of warm air through the outer compartment was prevented by maintaining a rapid (30 liters per minute) flow of air in the reverse direction. In experiments in which this cannula was used, it was necessary to interrupt the cold air stream at frequent intervals (about once every five minutes) to prevent blockade of the outer compartment and insulation of the laryngeal thermocouple by ice formed by the condensation and congelation of moisture from the exhaled air.

The midoral cannula (fig. 2) which was used in the second series of experiments was constructed in such a manner that both the cold air for inhalation and the warm exhaled air passed in and out of the mouth through the same compartment. Between respirations the air contained by the intraoral element of the cannula was relatively stagnant. During inspiration cold air was drawn out of the main air stream which was passing through the vertical element of the cannula. During expiration the warm exhaled air joined the cold air stream and was discharged with it through the upper orifice of the vertical element. A ball valve at the upper orifice of the vertical element prevented the ingress of warm air during inspiration. Actually the rate of flow of cold air through the vertical element was sufficient to prevent inspiration of warm air even if the ball valve had not been there.

Sensitive copper-constantan thermocouples constructed of 40 gage wire were introduced into the air stream at the various locations indicated in figures 1 and 2. These thermocouples either were provided with rigid supports or were enclosed in wire cages so as to insure their being free in the air stream and having no contact with the wall of the airway. The thermocouples measuring the temperature of the external air stream were not exposed to sudden changes in temperature and were therefore connected with an ordinary potentiometer. The thermocouples which were exposed to the respiratory fluctuations in temperature were connected in the first 3 experiments with a Mohl galvanometer having a period of 0.16 second and in subsequent experiments with a General Electric recording galvanometer having a period of 0.2 second. Rectal temperatures before, during and after inhalation of cold were determined by a mercury thermometer.

In the first 3 experiments ethyl carbamate was used as an anesthetic agent, and in all 3 instances the animals died between two and six hours after induction of anesthesia. In subsequent experiments anesthesia was induced by intravenous injections of phenobarbital sodium.

In 2 experiments, 597 and 598, a continuous record of the rate and amplitude of respiratory excursions as well as of heart rate and blood pressure were made. In 2 experiments, 592B and 638, samples of venous blood were taken before, during and after inhalation of cold for determination of oxygen, carbon dioxide, p_H, cell volume, red blood cell count, white blood cell count and differential blood count.

RESULTS OF EXPERIMENTS

As indicated in table 1, the animals breathed air that emerged from the cooling system at a temperature of approximately —100 C. for periods ranging between twenty and one hundred and thirty-three minutes.

TABLE 1.—*Ranges of Temperature of Air Inhaled*

Experiment Number	Site of Primary Impact of Cold Air	Length of Time That Animal Breathed Cold Air, Min.	Average External Temperature of Air Stream, C.	Temperature of Air at Different Levels Between Mouth and Lungs, C.				
				Larynx, Lowest Inspiratory Nadir	Midtrachea (10 Cm. Below Larynx)		Lower End of Trachea (22 Cm. Below Larynx)	
					Lowest Inspiratory Nadir	Average Expiratory Peak	Lowest Inspiratory Nadir	Average Expiratory Peak
593	Intralaryngeal	20	—100	—40	....	....	+30	+39
626	Intralaryngeal	20	—100	—40	....	....	+27	+39
598	Intralaryngeal	20	—100	—30	....	....	+18	+39
592A	Intralaryngeal	40	—100	—28	....	....	+23	+37
635A	Intralaryngeal	40	—100	—50	....	....	+23	+38
597	Intralaryngeal	20	—100	—37	....	....	+25	+39
592B	Midoral	5	+ 25	....	....	....	+38	+39
		48	—100				+20	+37
638	Midoral	5	+ 20	.. .	+30	+37	+37	+39
		6	— 40		+27	+37	+27	+39
		17	— 65		+23	+33	+26	+37
		42	—100		+18	+33	+23	+37
635B	Midoral	133	—100	....	+18	+36	+21	+38

In the first series of experiments (cannula 1) the temperature of the inhaled air was measured at the larynx and at the bifurcation of the trachea. Despite the fact that the air had been conducted from the cooling system to the larynx through a vacuum-jacketed tube, its temperature had been raised from —100 to between —50 and —28 C. by the time it reached the larynx. The coldest inspiratory nadir observed in any animal at the orifice of the laryngeal cannula was —50 C. In 1 animal (592A), —28 C was the lowest temperature recorded at the laryngeal orifice. It was characteristic that the lowest inspiratory temperatures recorded by the laryngeal thermocouple occurred during the first

two or three minutes after the flow of the cold air stream was started. Subsequent condensation and freezing of moisture from the exhaled air in the laryngeal orifice of the cannula was indicated first by lack of responsiveness of the thermocouple and later by actual obstruction to the flow of air.

By the time that the inhaled cold air reached the bifurcation of the trachea it had been warmed to a level well above freezing. Thus the lowest inspiratory nadir registered by the thermocouple at the bifurcation of the trachea was + 18 C. This occurred in an animal whose lowest inspiratory nadir at the larynx was — 30. It is of interest that in another animal (593) in which repeated laryngeal inspiratory nadirs of — 40

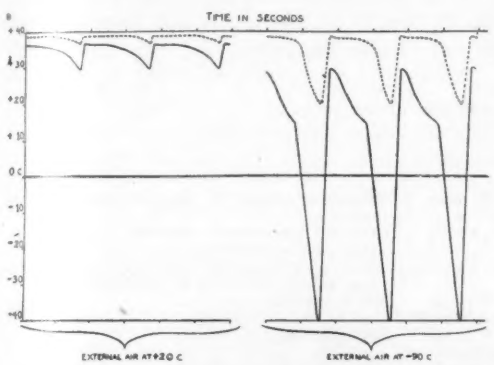

Fig. 3.—Changes in temperature in the upper and lower portions of the trachea of a dog during the inhalation of warm (+ 20 C.) and cold (— 90 C.) air. Dotted line indicates temperature changes at bifurcation of trachea; solid line, temperature changes in laryngeal orifice of cannula.

were observed the temperature at the bifiurcation of the trachea was never observed to drop below + 30 C. The slightness of the fluctuations in temperature recorded by the tracheal thermocouple in this animal may have been due to early plugging of the interstices of the guard cage by mucus. In all of this group of animals the air leaving the lungs was within 1 or 2 degrees of normal. Differences this small were not considered to be significant in view of the fact that they lay within the tolerance of the recording instruments.

In the second series of experiments shown in table 1 the cannula terminated about halfway between the front teeth and the larynx. In these experiments the animal's nose and mouth were bandaged with sheet rubber in such a way that no air could pass into or out of the lungs except by way of the cannula. It had been anticipated that in these experiments the air would be warmer at the bifurcation of the trachea than it had been in the first series of animals. Despite the fact that air inhaled through this cannula must have been warmed to some extent by the back of the mouth before it reached the larynx, the inspiratory nadirs at the bifurcation of the trachea did not differ significantly from those observed in the first series of experiments.

Characteristic segments of the temperature changes recorded by the laryngeal and deep tracheal thermocouples during the breathing of warm and cold air are shown in figure 3. These examples were selected from the galvanometer recording of experiment 635A, in which the transoral cannula shown in figure 1 was used. In the original record the readings from the two thermocouples were recorded alternately rather than simultaneously.

When air at room temperature (+ 20 C.) was breathed, thermal fluctuations in the lower part of the trachea were perceptible only during the first few minutes. Later when the wall of the cannula had been warmed by contact with the oral mucosa and the exhaled air, the inspiratory depressions in temperature in the trachea became imperceptible except when abnormally deep breathing was stimulated by the mixture of carbon dioxide with the entering air stream.

When cold air (— 100 C. in the external segment of the cannula) was breathed, the differences between the inspiratory nadirs in the larynx and in the deep trachea became much more pronounced. Although the air temperature in the laryngeal orifice of the cannula (fig. 3) fell to — 40 C., the air had been warmed to approximately + 20 C. by the time it reached the bifurcation of the trachea. The lowest air temperature in each situation was registered at the end of inspiration and the highest at the end of expiration. A noteworthy characteristic of the intralaryngeal inspiratory nadir is the shortness of the time during which the mucous membrane was exposed to a freezing temperature. For a period lasting approximately half a second during the latter part of each inspiration the air temperature in the larynx fell below 0 C. Immediately before and after such nadir the temperature was well above freezing. It appears that the breathing of cold air may cause a momentary exposure of the mucosa of the larynx and upper trachea to a freezing temperature but that the temperature at the bifurcation of the trachea is not likely to approach a cell-killing level of coldness at any time.

Fig. 4.—Obstructive edema of the pharynx and larynx due to prolonged direct exposure to cold (experiment 593).

ferential count. It should be noted, however, that in no instance were the observations continued later than one hour after the animals' exposure to cold.

So far as the clinical behavior of the animals was concerned, the only observable ill effect of the inhalation of the cold air was early hyperactivity of the mucous glands of the upper respiratory tract, with coughing and hoarseness of some of the animals during the first twenty-four hours. All animals permitted to survive twenty-four hours or longer were lively, happy and not significantly disturbed by the experimental procedure.

Postmortem pathologic studies (table 2) were made of 7 animals after postexposure intervals ranging between two and a half and forty hours. In the case of the two and a half hour recovery period (593), the animal did not regain con-

TABLE 2.—*Clinical and Pathologic Observations*

Experiment Number	Clinical Behavior After Inhalation of Cold Air	Postexposure Period	Principal Pathologic Changes
593	Obstructive edema of pharynx and larynx *	2½ hours	Obstructive edema of pharynx and laryngeal orifice
626	Excessive secretion of mucus from upper air passages	4 hours	Catarrhal sublaryngeal tracheitis; patchy atelectasis and emphysema
598A	Excessive secretion of mucus from upper air passages	5 hours	Catarrhal and membranous sublaryngeal tracheitis; patchy atelectasis and emphysema
592A	Excessive secretion of mucus for 12 hours; hoarse for 2 days; normal after second day	Survival experiment	Not determined
635A	Excessive secretion of mucus for 12 hours; hoarse for 2 days; normal after second day	Survival experiment	Not determined
597	Excessive secretion of mucus for 12 hours	12 hours	Catarrhal sublaryngeal tracheitis; patchy atelectasis and emphysema
592B	Normal	24 hours	Severe catarrhal laryngitis and sublaryngeal tracheitis; patchy atelectasis and emphysema
638	Excessive secretion of mucus for 12 hours; hoarse but otherwise normal	24 hours	Severe catarrhal and membranous sublaryngeal tracheitis; patchy atelectasis and emphysema with focal pneumonitis
535B	Excessive secretion of mucus; hoarse for 24 hours; normal after second day	40 hours	Mild sublaryngeal tracheitis; no abnormality of lungs

* Projecting 1.5 cm. beyond the vacuum jacket, the laryngeal end of the cannula had a solid glass wall. In experiment 593 the mucosa of the pharynx and larynx was in direct contact with this cold segment of glass. In subsequent experiments the tip of the cannula was wrapped with insulating material to reduce heat transfer at this site.

In no animal was a drop in rectal temperature observed during or after the inhalation of cold air.

In neither of the 2 animals (597 and 598) for which kymographic recording of blood pressure and respiration was made was any striking change observed. There occurred an evanescent rise in systolic pressure and a slight increase in the rate and amplitude of the respiratory excursions of the thorax.

In neither of the 2 animals (592B and 638) from which samples of venous (femoral) blood were taken before, during and immediately after inhalation of cold air were significant disturbances observed in the oxygen or carbon dioxide saturation, the p_H, the cell volume, the red blood cell count, the white blood cell count or the differential count.

sciousness from the anesthetic and died as a result of obstructive edema of the pharynx and larynx (fig. 4). The edema developed rapidly, and although the obstruction was recognized and relieved by intubation approximately two hours after exposure, the animal was already anoxemic beyond recovery. As previously indicated, the edema in this animal was caused by direct contact of the cold tip of the laryngeal cannula with the adjacent tissues. Obstructive edema was not observed in any of the succeeding experiments, in which the tip of the cannula was wrapped with insulating material. In this animal (593), the mucous membrane of the pharynx adjacent to the larynx had been in continuous contact with cold glass for twenty minutes. Wherever mucosal attachments permitted the

accumulation of interstitial fluid there was massive edema (fig. 5). Although the animal died two and a half hours after exposure to cold, widespread necrosis of the glandular epithelium and muscle of the pharynx had occurred. The stratified epithelium covering the surface appeared intact and showed remarkably little cytologic evidence of injury. In some situations it was elevated by subepithelial collections of free fluid in the form of large and small vesicles. The subjacent tissues were hyperemic, hemorrhagic and sparsely infiltrated by polymorphonuclear leukocytes. No thrombosis was observed. Other than hyperemia through its upper third, the tracheal mucosa showed no significant abnormality. The lungs were normal.

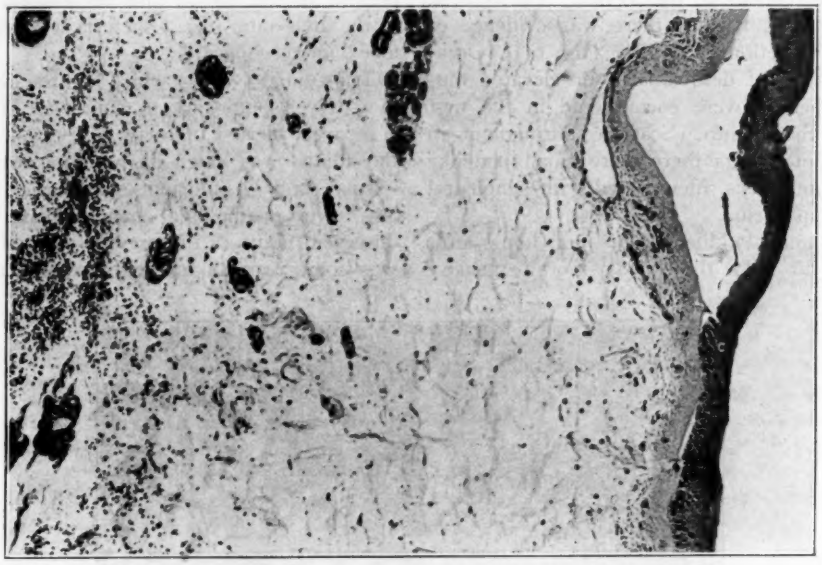

Fig. 5.—Photomicrograph showing hemorrhagic edema of the pharyngeal mucosa caused by direct exposure to cold (experiment 593). Magnification × 100.

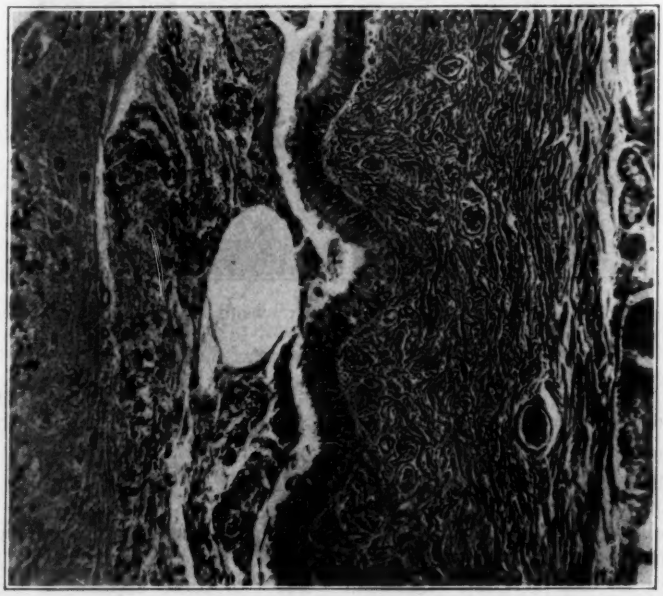

Fig. 6.—Photomicrograph showing catarrhal inflammation of the mucous membrane of the upper portion of the trachea four hours after inhalation of cold air (experiment 626). Magnification × 100.

Between four and twelve hours after exposure there was more definite evidence of tracheitis. In the animals killed at this time there was some edema of the mucous membrane of the ventricular recesses of the larynx. Throughout the larynx and trachea there was evidence of excessive secretion of mucus (fig. 6.) Occasional patches of desquamated or elevated mucosal epithelium were encountered in the first 10 cm. of the trachea. Scattered throughout all lobes of both lungs there were small platelike zones of atelectasis interspersed with subpleural foci of emphysema.

In both animals killed twenty-four hours after exposure to cold there was more extensive mal was the amount of atelectasis great enough to interfere significantly with the respiratory exchange. In 1 animal (638) occasional collections of polymorphonuclear leukocytes were present in the alveoli and bronchioles of some of the atelectatic foci. Bacteria were not recognized microscopically.

The animal (635B) which had the longest and most severe exposure to cold was killed after a recovery period of forty hours. At the time the animal was killed its behavior was entirely normal, and postmortem examination disclosed less severe pathologic changes than had been observed in any of the previous animals. There was some residual tracheitis, as indicated by a

Fig. 7.—Photomicrograph showing severe sublaryngeal tracheitis twenty-four hours after inhalation of cold air (experiment 638). Magnification × 100.

damage of the superficial epithelium of the larynx and sublaryngeal portion of the trachea. There was nonobstructive edema of the mucosa lining the ventricular recesses. Patches of membrane composed of tenacious mucus and desquamated epithelial cells were adherent to the mucosa of the larynx and upper part of the trachea (fig. 7). In neither animal was there any significant gross or microscopic abnormality of the lower portion of the trachea or of the primary bronchi. Occasional small plugs of mucus mixed with desquamated epithelial cells were found in some of the smaller bronchi. The distribution of atelectasis and emphysema was similar to that described in preceding animals. In neither animal exudative reaction. There was no longer any evidence of excessive secretion of mucus, and whatever atelectasis and emphysema may have been present during the first twenty-four hours had now disappeared. No abnormality of the lungs was recognized microscopically.

Microscopic examination of the respiratory tracts of these animals at varying times after exposure to cold disclosed certain differences in the susceptibility of mucosal epithelium to thermal injury. The stratified epithelium of the mouth and, to a lesser extent, that of the pharynx and larynx were less susceptible to injury by cold than was the columnar epithelium of the upper portion of the trachea. In

instance was there evidence of epithelial injury of the mouth, despite the fact that in the second series (fig. 2) the primary impact of the cold air occurred in the midoral region. With the exception of animal 593 (noninsulated cannula) there was no subject in which necrosis of the laryngeal mucosa could be ascribed to thermal injury. Although the temperature to which the upper tracheal mucosa was exposed was undoubtedly lower than that to which the back of the mouth and larynx were exposed, there were several instances in which extensive epithelial destruction was observed in the former situation.

COMMENT

The inhalation of extremely cold air by dogs for periods ranging between twenty and one hundred and thirty-three minutes caused a catarrhal, and in some instances a membranous, tracheitis but failed to produce significant injury of the lower air passages or lungs. The temperature of air taken into a transoral cannula at — 100 C. rose to between — 50 and — 28 by the time it reached the larynx and between + 18 and + 30 C. by the time it reached the lungs.

The results of this experimental investigation invite a consideration of the circumstances in which the exposure of living tissue to cold may result in cellular injury and in death. So far as in vitro observations are concerned, it has been shown both by Lambert [1] and by Fischer [2] that chilling is not likely to cause primary cellular injury unless the fall in tissue temperature is such that cells are disrupted by the formation of ice crystals. Similar conclusions were reached by Lewis [3] from experiments performed in vivo on human skin. That intracellular congelation is not always prerequisite to injury by cold may be inferred from recent studies of immersion foot.[4] In this type of injury ischemic necrosis of an extremity, presumably due to the thermally induced neurocirculatory disturbances, may follow prolonged exposure to wetness and cold even though the tissue is at no time frozen.

Thus it appears that tissue may sustain primary injury if it is frozen or secondary injury without freezing if the exposure to cold is long enough to lead to a persistent disturbance in circulation.

When account is taken of the extremely low heat capacity of dry air, the nonoccurrence of primary pulmonary injury following the breathing of cold air is in no sense surprising. Volume for volume, water in a liquid state liberates about four thousand times as much heat energy for each degree it cools as does air. Thus, since water and protoplasm have about the same heat capacity, the number of calories required to raise 500 cc. of air from an inhalation temperature of — 40 C. to an exhalation temperature of + 40 C. would be furnished by the heat given off by about 1 Gm. of tissue, incident to a drop of 10 degrees in its temperature. Actually the number of calories lost by the respiratory mucosa incident to the warming of 500 cc. of air under such conditions would probably be greater than 10, because the air would be relatively dry when inhaled and saturated with moisture when exhaled. The additional heat loss by the mucous membrane incident to the vaporization of this amount of moisture would bring the total deficit in such circumstances to approximately 20 calories per respiration. In consideration of the fact that these 20 calories could be supplied by the cooling of 1 Gm. of tissue by approximately 20 degrees centigrade, no great amount of primary pulmonary injury due to the inhalation of cold air is to be expected.

The extent to which the evidence provided by these experiments can be applied to man should be considered. It is a fact that the trachea of a dog is long and narrow compared with that of man. It cannot be stated that because inhaled air is warmed from — 50 at the larynx to + 23 at the bifurcation of the trachea in the dog the same degree of warming would occur in man. It does seem likely, however, that these anatomic differences in dog and man would be more than offset by the fact that the cold air was conducted directly to the larynx of the dog by means of an insulated cannula, whereas in nonexperimental conditions man would have the added protection of his oral or nasal mucosa. It is also a fact that the rate of heat loss by the air passages would be augmented by rapid or deep breathing. Even if the rate were doubled or tripled, the total would not be impressive as a cause of direct pulmonary injury.

Although it may be inferred from these experimental results that intrapulmonic air temperatures much lower than + 20 C. are not likely to occur in man in nonexperimental conditions, nothing is known regarding the relative susceptibilities of man and dog to reflex circulatory or other disturbances which may occur in such circumstances. However, there was no indica-

1. Lambert, R. A.: J. Exper. Med. **18**:406, 1913.
2. Fischer, A.: Arch. f. exper. Zellforsch. **2**:303, 1926.
3. Lewis, T.: Brit. M. J. **2**:795, 1941.
4. Blackwood, W.: Brit. J. Surg. **31**:329, 1944. White, J. C., and Warren, S.: Causes of Pain in Feet After Prolonged Immersion in Cold Water, War Med. **5**:6 (Jan.) 1944.

tion, so far as the dog is concerned, of any local or general reflex disturbance caused by the inhalation of cold air. No attempt was made during this investigation to determine the extent to which the chilling of the upper respiratory mucosa may have altered its resistance to bacterial invasion.

A recent report by Smith [5] calls attention to a syndrome of pain in the chest, cough, hemoptysis, patchy pulmonary consolidation and fever seen occasionally in flying personnel after high altitude missions in which intensely cold air was breathed. No pathologic studies of the condition are available. Smith stated that recovery generally occurred between ten days and two weeks after exposure.

On a basis of the experiments with animals reported here, it is a fair inference that the disturbances described by Smith were due to an acute thermally induced hemorrhagic tracheitis with a certain amount of secondary atelectasis and pneumonitis probably caused by the aspiration of masses of mucus and desquamated tracheal mucosa. It is reasonable to believe that persons who have sustained such injury may be rendered more than normally susceptible to infection of the respiratory tract.

That man can breathe extremely cold air without sustaining pulmonary injury is indicated by a recent case at the Valley Forge Hospital.[6] In November 1943, an aviator, while on duty in a gun turret, was wounded by a high explosive missile which also destroyed most of his protection against the cold air. For a period of about three hours he was exposed head foremost to a stream of air moving at the rate of 160 miles (258 kilometers) per hour and having a temperature of approximately — 50 C. When he was admitted to the hospital, his face and fingers were frozen. Approximately six hours after his admission an obstructive edema of the mucous membranes of his mouth, nose and pharynx developed. An airway was established by means of a tracheotomy. He subsequently lost his fingers and much of the soft tissue of his face as a result of freezing. Despite an exposure to cold that led to an obstructive edema of his external respiratory passages, there was at no time evidence of injury to his bronchi or lungs, and he made an uneventful convalescence as far as pulmonary complications were concerned.

5. Smith, S.: Air Surgeon's Bull. (no. 6) **1**:17, 1944.
6. Milligan, C. B., Capt., M.A.C.: Personal communication to the authors.

SUMMARY

In this investigation dogs were caused to breathe extremely cold air for periods ranging between twenty and one hundred and thirty-three minutes. The rate at which air was warmed within the body was measured by means of appropriately placed thermocouples. The air was delivered to the larynx at temperatures which ranged between — 50 and — 28 C., and in no instance were temperature recordings lower than + 18 C. observed at the bifurcation of the trachea.

The inhalation of cold air in circumstances such that intralaryngeal inspiratory nadirs as low as or lower than — 30 C. were reached resulted in the development of a localized sublaryngeal tracheitis. In some animals the disturbance was limited to unusual activity on the part of the mucous secreting glands, and in others there was focal destruction of the superficial epithelium. In no instance was there evidence of primary injury to the lower portion of the trachea, the bronchi or the lungs.

The aspiration of mucus or mucus and mucosal detritus from the upper portion of the trachea may result in the development of small and evanescent foci of pulmonary emphysema and atelectasis.

The explanation of the rapid warming of inhaled cold air and of the occurrence of relatively mild and localized injury following the inhalation of cold air lies in the fact that dry air has an extremely low heat capacity and that the number of calories required to produce a great rise in the temperature of dry air can be provided by the heat derived from the cooling of a small amount of tissue by a few degrees.

Although the intermittent exposure to cold air that occurs during normal respiration does not cause significant injury to the pharynx or larynx, a continuous exposure of these structures to cold may result in the development of a rapidly obstructive edema.

Experiments on dogs warrant the inference (*a*) that it is unlikely that significant injury to the air passages of man would result from the breathing of air at any degree of coldness likely to be encountered in nonexperimental conditions so long as it was inhaled through the nose or between partially closed lips and (*b*) that even though extremely cold air were inhaled rapidly through a widely opened mouth, it would be warmed to a point well above freezing by the time it reached the bronchi.

FATAL POISONING FROM POTASSIUM THIOCYANATE USED IN TREATMENT OF HYPERTENSION

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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During the last decade a revived interest in the treatment of arterial hypertension with thiocyanates, with varying degrees of success, has occurred. The toxic properties of these drugs have been known since the pharmacologic observations of Claude Bernard in 1857.[1] Their noxious effects have been well recognized in recent years.[2] The Council on Pharmacy and Chemistry of the American Medical Association has not accepted them and even has advised against their use.[3]

Great progress in the field was made by Barker in 1936 [2f] with the introduction of the practice of determining serially the blood content of thiocyanates. It was thought that with this method toxic blood levels, and therefore deleterious side effects, could be avoided. A few instances of serious and even fatal intoxication, however, have been recently reported. We have, unfortunately, had 1 such instance out of a series of 73 cases in which potassium thiocyanate was used.[4] We feel that the report of cases like our own is necessary in order to speed the final and correct evaluation of this form of treatment.

The few cases hitherto published of death due to the therapeutic use of these drugs have presented a fairly uniform sequence of events.[5] Often a high degree of asthenia precedes the onset of symptoms. These are initiated with dysarthria and sometimes verbal aphasia and are followed by mental dulness, clonic contractures of the extremities and a deliriant state with visual or auditive hallucinations, sometimes with great mental and motor excitation. In fatal cases, despite the discontinuance of the drug with the onset of symptoms, there is a downhill course, with accentuation of the mental confusion, convulsions, stuporous state, coma, sphincter incontinence, collapse and death three to nineteen days from the beginning of symptoms.

REPORT OF CASE

A. G., a white man aged 55, was admitted to the Hospital on May 17, 1943, complaining of dyspnea on exertion, tinnitus, photopsies and occurrence of palpitation during the preceding three months. He had also been suffering from muscular weakness, paresthesia in the right upper extremity and orthopnea during the month preceding admission. His past history was irrelevant except for an immoderate use of alcohol throughout most of his adult life and for a tendency to repeated nosebleeds for the past several years.

Physical examination disclosed a plethoric patient with a blood pressure of 230 systolic and 130 diastolic and with mild signs of congestive heart failure as indicated by the presence of dyspnea, slight cyanosis of the lips, tachycardia, pulmonary congestion, enlargement of the left side of the heart and some edema of the ankles. The liver was not remarkable, and ascites was not detected. A slight degree of dysarthria was present. The diagnoses of essential arterial hypertension, generalized arteriosclerosis of moderate degree and congestive heart failure were made.

From the Clínica Médica del Hospital San Francisco de Borja, Escuela de Medicina de la Universidad de Chile (Prof. A. Garretón-Silva), Santiago, Chile.

1. Bernard, C.: Leçons sur les effets des substances toxiques et médicamenteuses, Paris, J. B. Baillière et fils, 1857, p. 354.

2. (*a*) Wald, M. H.; Lindberg, H. A., and Barker, M. H.: The Toxic Manifestations of Thiocyanates, J. A. M. A. **112**:1120-1124 (March 25) 1939. (*b*) Goldring, W., and Chasis, H.: Thiocyanate Therapy in Hypertension: Observations on Its Toxic Effects, Arch. Int. Med. **49**:321-329 (Feb.) 1932. (*c*) Garvin, C. F.: The Fatal Toxic Manifestations of the Thiocyanates, J. A. M. A. **112**:1125-1127 (March 25) 1939. (*d*) Lindberg, H. A.; Wald, M. H., and Barker, M. H.: Observations on the Pathologic Effects of Thiocyanate, Am. Heart J. **21**:605-615 (May) 1941. (*e*) Healy, J. C.: Therapeutics and Toxicology of Sulfocyanates, New England J. Med. **205**:581-583 (Sept. 17) 1931. (*f*) Barker, M. H.: Blood Cyanates in Treatment of Hypertension, J. A. M. A. **106**:762-767 (March 7) 1936.

3. Elixir Kacyan McNeil and Tablets Kacyan McNeil Not Acceptable for N. N. R., report of the Council on Pharmacy and Chemistry, J. A. M. A. **92**:1838 (June 1) 1929.

4. del Solar, A.; Dussaillant, G., and Rodríguez, G.: El tratamiento ae la hipertensión arterial con el tiocianato de potasio, Rev. méd. de Chile **72**:663-675 (Aug.) 1944.

5. Russell, W. O., and Stahl, W. C.: Fatal Poisoning from Potassium Thiocyanate Treatment of Hypertension, J. A. M. A. **119**:1177-1181 (Aug. 8) 1942.

Further study showed a brachial venous pressure of 11.5 cm. of water, a vital capacity of 1,800 cc. and the circulatory rate of the blood from arm to lung (ether) and from arm to tongue (calcium bromide) moderately prolonged, being twelve and twenty-two seconds respectively. The electrocardiogram showed signs of probable left ventricular hypertrophy and myocardial damage. The ocular fundi showed moderate retinal arteriolosclerosis and venous engorgement. Roentgen examination disclosed an aortic type of heart, with moderate enlargement and an atheromatous aortic pattern. Results of laboratory studies were essentially normal except for an occasional red blood cell and traces of albumin in the urine. The blood urea nitrogen level was 14 mg. per hundred cubic centimeters. The blood sugar and total cholesterol levels and the sedimentation rate were normal. There was no anemia. A test of the urea clearance of the blood gave a value of 96 per cent of normal.

Hospital Course (fig. 1).—The usual treatment of congestive heart failure, including rest in bed, diet and use of digitalis, xanthines and sedation, resulted in a prompt restoration of circulatory function. However, in spite of prolonged rest in bed and antispasmodic therapy, the blood pressure persisted constantly elevated, above 200 mm. systolic and 102 mm. diastolic. On July 6 it was decided to try potassium thiocyanate, 0.50 Gm. daily in three doses being indicated. This was increased to 0.60 Gm. eleven days later; the blood content of thiocyanate, however, remained low. On July 22 it was only 2.53 mg. per hundred cubic centimeters, and consequently the prescribed dose was again raised, to 0.90 Gm. daily. Six days later, on July 28, mental dulness and increased dysarthria were noted. A slight reduction of blood pressure, to 185 mm. systolic and 110 mm. diastolic, was recorded; physical examination disclosed no other changes. Use of thiocyanate was discontinued immediately; during the day the patient complained of zoopsia, and slight clonic contractures of the upper extremities were noted. The thiocyanate level of the blood[6] as determined in the morning of that day was 7 mg., but eight hours later it had risen to 29 mg. per hundred cubic centimeters and the urinary concentration of the drug was 33 mg. per hundred cubic centimeters.

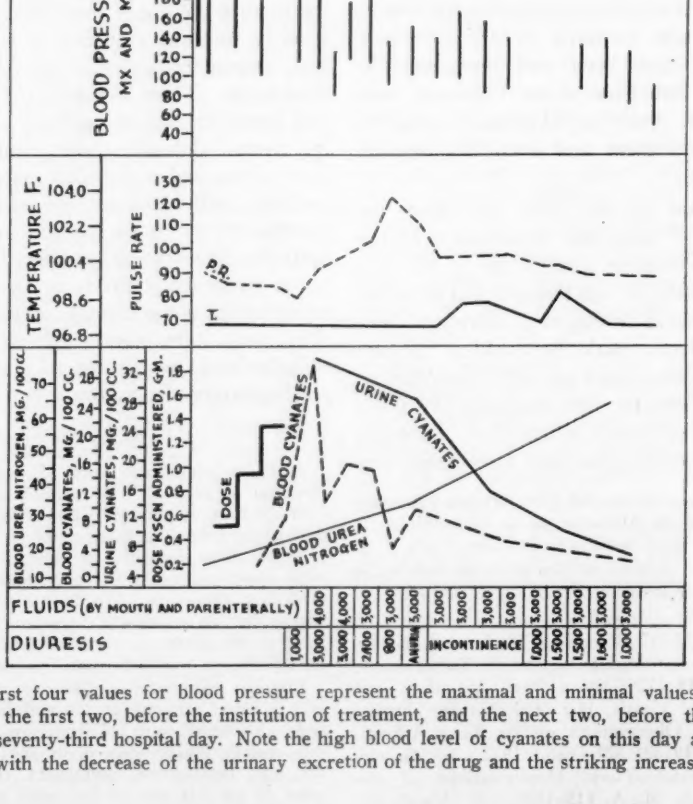

Fig. 1.—The first four values for blood pressure represent the maximal and minimal values for diastolic and systolic pressures; the first two, before the institution of treatment, and the next two, before the onset of toxic symptoms, on the seventy-third hospital day. Note the high blood level of cyanates on this day and its subsequent descent, together with the decrease of the urinary excretion of the drug and the striking increase of urea nitrogen in the blood.

We discovered that eight to ten days previously the patient had broken the tip of the dropper with which he measured the solution of the drug to be taken and had disregarded this accident. We could calculate then that when we had prescribed 0.60 Gm. of potasium thiocyanate the patient had been ingesting 0.89 Gm. daily and that when the prescribed dose had been raised

6. The values obtained were repeatedly checked on the same specimen of blood.

to 0.90 Gm. he had begun to take about 1.34 Gm. per day. Because of this and because of the clinical picture already described, the diagnosis of potassium thiocyanate intoxication was made. A high fluid intake and sedation with bromides were indicated. The following day the same abnormal signs somewhat more accentuated were observed, and, in addition, occasional deliriant episodes were noted. Cutaneous and tendinous reflexes were increased, and mild motor incoordination of the limbs, more pronounced in the right leg, was detected; the pulse rate was 96 per minute and the blood thiocyanate level 8.75 mg. per hundred cubic centimeters.

In an attempt to increase the elimination of the drug and to minimize its deleterious effects on cellular respiration, the following therapeutic scheme was instituted: withdrawal of 600 cc. of venous blood; continuous intramuscular injection of isotonic dextrose solution and administration of fluids by mouth freely, a total of 4 liters in the day being attained; 2 cc. of esidrone (the sodium salt of pyridenedicarboxyl-β-mercuri-ω-hydroxypropylamide theophylline) intramuscularly, 75 mg. of thiamine hydrochloride and 300 mg. of nicotinamide in divided doses intravenously, 300 mg. of ascorbic acid and 0.20 Gm. of digitalis leaf (maintenance dose) by mouth were also administered.

During the following days this treatment was completed with the addition of aminophylline, metrazol and nikethamide as respiratory stimulants and administration of riboflavin (3 mg. per day) parenterally and adequate amounts of fluid was continued. Few changes were observed in the condition of the patient until the fourth day of intoxication, when he fell into a comatose state with tachycardia and Cheyne-Stokes respiration; no additional changes were noted in the fundi. A spinal tap was performed and 10 cc. of fluid of normal appearance was withdrawn; chemical examination disclosed a thiocyanate content of 10 mg. per hundred cubic centimeters, 0.1 per cent albumin with 1 white blood cell per cubic millimeter and 0.64 per cent chlorides; the fluid was otherwise normal. Neurologic examination disclosed the presence of a slight spastic right hemiparesis; the neurologists'[7] opinion was that the patient had essentially the picture of a toxic encephalopathy and, in addition, slight signs of focal damage in the left hemisphere, and they suggested that these might correspond to an old lesion that had been made more prominent by the encephalic intoxication itself. They considered other possibilities, i. e., a meningocortical hemorrhage or other acute vascular accident, as remote. The same conditions were found and the same diagnosis was maintained on subsequent neurologic examinations.

On the fifth day of illness the patient recovered consciousness and blood pressure readings showed a decided drop, to 130 mm. systolic and 90 mm. diastolic. No additional changes were noted in the ocular fundi; a complete blood count exhibited normal values for hemoglobin and erythrocytes and a hyperleukocytosis (16,500 cells) with strong hyperregenerative deviation to the left. The next day aminophylline, analeptics, thiamine hydrochloride and riboflavin were discontinued and hypertonic dextrose solution intravenously was prescribed to overcome a state of anuria that had appeared in the morning of that day and that lasted twenty-four hours.

Except for the appearance of some pitting edema in the legs, no significant changes were noted on subsequent days. On August 5 the total cholesterol level, found to be 148 mg. on admission, had fallen slightly, to 130 mg. per hundred cubic centimeters of blood. A similar fall of blood protein to slightly subnormal values was also noted; the value on August 11 was 5.44 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.2. On August 10, the fourteenth day of illness, the patient again became deeply stuporous; physical examination showed signs of bronchopneumonia in the base of the right lung. Finally, on the sixteenth day, the patient's condition became critical. Blood pressure values of only 95 mm. systolic and 50 mm. diastolic, pronounced stertorous dyspnea and relaxation of sphincters supervened. He died in collapse in the morning of that day.

Necropsy.[8]—The significant observations were as follows:

Gross Examinations: In the brain there was a small area, the size of a nut, of very recent hemorrhagic encephalomalacia in the left occipital lobe. In addition to this, two 3 by 1 by 1 cm. areas of old and well

Fig. 2.—Section from a kidney. Hematoxylin and eosin stain; × 200.

capsulated encephalomalacia were also found, one in the white matter close to the external aspect of the right lenticular nucleus and the other in the left hemisphere involving the external face of the optic thalamus and part of the anterior arm of the internal capsule. There existed decided arteriosclerosis at the base of the brain. The heart was moderately enlarged and hypertrophic, with a small patent foramen ovale, coronary arteriosclerosis and slight diffuse myocardial scarring of vascular type. In the aorta atheromatous plaques in moderate number were observed. The right kidney weighed 200 Gm.; the left, 230 Gm. The surface was finely granular, with a small number of scars of vascular type; renal arteriosclerosis was observed. Confluent bronchopneumonia of the lower lobe of both lungs was found. Hyperplasia of the prostate with hypertrophic bladder muscle and an isolated gallbladder stone were observed.

7. Drs. E. Uiberal and R. Nuñez B. assisted as consultant neurologists.

8. Prof. H. Rodríguez H. and Dr. C. Medina L. made the complete pathologic study in this case.

Microscopic Examinations: Sections from both the damaged and the undamaged areas in the brain, heart muscle, liver, lungs, kidneys and bone marrow failed to disclose specific alterations ascribable to the drug. On the periphery of the right occipital lobe softening, inflammatory infiltration and neuroglial proliferation of slight degrees and few macrophages, some containing lipid droplets and hemosiderin inclusions, were found. Sections from the kidneys showed a diffuse and irregular inflammatory infiltration of mononuclear and polymorphonuclear cells with occasional involvement of the glomeruli, most of which, nevertheless, appeared normal. There were occasional hemorrhagic interstitial foci. Small and medium-sized arteries appeared thickened by a process of obliterating endarteritis that, in correspondence with some small atrophic foci, completely occluded the vessel. The more prominent changes, however, were found in the convoluted tubules, especially in the proximal ones; they consisted in a marked cloudy swelling and frequently even necrosis of their epithelial lining, with coagulated albuminous material, degenerated epithelial cells and erythrocytes in their lumen (fig. 2). These changes presented varying degrees of intensity in different sections. Calcic casts, especially in the collecting tubules, were also found. Sections from the liver, bone marrow and other organs disclosed no significant changes.

Table 1 shows the amounts of thiocyanate contained in different tissues of our patient [9] compared with the values obtained in the other 2 cases of fatal poisoning in which such study has been performed.[10] It can be seen that in our case there was a fairly uniform distribution of thiocyanate in the tissues and the values were distinctly higher than in the other 2 cases.

TABLE 1.—*Amounts of Drug in the Tissues in 3 Cases of Fatal Potassium Thiocyanate Poisoning*

Author	Potassium Thiocyanate, Mg. per 100 Gm.						
	Brain	Heart	Kidney	Liver	Lung	Muscle	Spleen
Goldring and Chasis, 1932.....	18.0	9.7	15.4	9.2	17.0	....	14.5
Russell and Stahl, 1942.....	....	4.2	5.4	10.1	....	....	....
Del Solar and associates, 1944..	22.1	28.6	25.5	26.3	22.0	16.5	....

COMMENT

The presence of the encephalic lesions already described might cast some doubt on the true cause of death in this patient. It should be pointed out, however, that two of the foci of encephalomalacia corresponded to old cicatricial "cured" lesions; therefore death cannot be ascribed to them alone. On the other hand, it is quite possible that an already damaged brain, with impaired blood supply, may represent a predisposing factor either for the establishment of the intoxication or for the fatal outcome of the case. In this connection it is interesting to point out that in Russell and Stahl's case [5] an area of old left temporal encephalomalacia was also found and that in 4 of the other 5 cases of fatal therapeutic poisoning as shown in table 2 as well as in the 4 cases of toxic encephalopathy in the series of Barker and associates [11] the patients were all elderly persons. If this assertion proves to be true, it will indicate a clearcut contraindication to the use of potassium thiocyanate for hypertension, since injury to the brain tissue of significant degree is a common and frequently unrecognizable feature in the natural history of this disease.

The problem concerning the third area of thrombotic softening in the right occipital lobe is simpler. This was a rather recent lesion, as evidenced by its macroscopic appearance and the slight inflammatory reaction and phagocytic activities on section, and consequently should be regarded as a terminal event, possibly precipitated by the great decline of blood pressure that occurred during the intoxication.

Some comment should be made regarding the necrotic nephrosis found in this case. No mention of damage to the renal parenchyma from potassium thiocyanate either in human subjects or in experimental animals has been encountered in a fairly comprehensive review of the literature.[4] Thus our case would appear as the first in the literature in which it has been observed. Some reservations must be made, however, relative to the use of a mercurial diuretic (esidrone) in the treatment of our patient. The possibility of death from mercurial poisoning must be considered. Although we could not say with certainty that the renal lesions were not due to the diuretic employed, we must point out that the picture presented by the patient during life was not at all the usual one observed in cases of mercurial poisoning or of mercurial nephrosis and repeated urinalysis showed no increase in the few red blood cells and the traces of albumin that the patient had shown since his admission to the hospital. Moreover, the conclusion that death may have been produced by a single small dose

9. For this determination an alcoholic extraction from the tissue was performed and the thiocyanate level determined by Barker's method but employing standard solutions prepared with alcohol.

10. Goldring and Chasis.[2b] Garvin.[2c] Russell and Stahl.[5]

11. Barker, M. H.; Lindberg, H. A., and Wald, M. H.: Further Experiences with Thiocyanates, J. A. M. A. **117**:1591-1594 (Nov. 8) 1941.

of esidrone [12] given intramuscularly appears unlikely in the light of present knowledge and according to the data recently compiled on the subject by DeGraff and Nadler.[13]

We state, therefore, that the excessive intake of the drug, together with the characteristic course and clinical features of the case and the high content of drugs in the blood, in the spinal fluid and most especially in the tissues, leaves us no doubt about the diagnosis of fatal thiocyanate poisoning. A survey of the literature shows that our patient is the seventh whose death was due to this form of treatment (table 2).

accordance with present knowledge, that this was not a suitable case for use of the drug. In our own case a distinct error in dosage appears as responsible for the death of the patient. The remaining case, reported by Garvin, appears therefore as the only one in which treatment was irreproachable, although the advanced age of the patient could be offered as an objection. It has been said,[14] and we agree with the statement, that potassium thiocyanate should not be administered to patients over 60 because of poor tolerance.

TABLE 2.—*Reported Cases of Fatal Poisoning from Thiocyanate*

Case	Author	Sex and Age	Dose, Gm.	Blood Thiocyanate, Mg. per 100 Cc.	Necropsy	Drug in Tissues, Mg. per 100 Gm.	Comment
1	Lesser, 1898 [5]	M, 58	? massive	..	Yes	Strong traces	Suicidal intent
2	Kobert, 1906 [2c]	F, ..	0.3	..	....	.....	Questionable; small dose; incomplete data
3	Vintilesco and Popesco, 1916 [2c]	M, 27	100 ?	Present	Yes	Present	Suicidal intent
4	Saleeby, 1930 [2a]	.. ..	0.3 daily	..	Yes	.....	Doubtful; coronary and mesenteric thrombosis
5	Healy, 1931 [2e]	F, 67	9 (total in 10 days)	..	....	.....	Therapeutic use
6	Healy, 1931 [2e]	F, 63	0.96 to 0.64 daily	..	....	.....	
7	Goldring and Chasis, 1932 [2b]	F, 40	9.7 in 15 days; 0.65 daily	..	Yes	9.2 to 18	Therapeutic use
8	Goldring and Chasis, 1932 [2b]	F, 56	14.5 in 18 days; 0.80 daily	..	....	.....	Therapeutic use
9	Garvin, 1939 [2c]	F, 71	9 in 15 days; 0.32 to 0.96 daily	13.6, 18.6	Yes	.....	Therapeutic use
10	Russell and Stahl, 1942 [5]	M, 52	5.6 in 14 days; 0.4 daily	15.2, 21.7	Yes	4.2 to 10.1	Therapeutic use
11	Del Solar, Dussaillant, Brodsky and Rodríguez, 1944	M, 55	18 in 22 days; 0.5 to 1.34 daily	7, 29	Yes	16.5 to 28.6	Therapeutic use; patient ingested more than prescribed dose

Table 2 presents a summary of the fatal poisonings hitherto reported. It can be seen that the first 3 cases represent instances of suicide or possibly of suicidal intent. The fourth case cannot be considered as an unquestionable instance of thiocyanate poisoning, since the toxic manifestations were mainly cutaneous, the dosage was small, determinations of thiocyanate were not done and, finally, death resulted from coronary and mesenteric thrombosis. The remaining 7 cases, including ours, appear, on the other hand, as genuine instances of fatal poisoning. In 4 of these (cases 5, 6, 7 and 8) no determination of blood thiocyanate level was done during the treatment and the doses employed appear excessive. Of the remaining 3 instances, in the case reported by Russell and Stahl before treatment there was a significant nitrogen retention, poor renal function and probably also some degree of congestive heart failure. We feel, in

It could be inferred that by strict observance of the indications for correct administration according to prevalent concepts serious and fatal intoxications could be avoided entirely. We feel, nevertheless, that this is not entirely true. Barker and associates [15] have stated that in their experience blood thiocyanate concentrations below 15 mg. per hundred cubic centimeters are innocuous and that serious reactions have been observed only with levels of 20 mg. or above. These contentions, on which rests all the rationale of potassium thiocyanate therapy, although applicable to the great majority of persons, cannot be generalized as a therapeutic rule. Page [16]

12. Two cubic centimeters of esidrone contain 0.086 Gm. of mercury.

13. DeGraff, A. C., and Nadler, J. E.: A Review on the Toxic Manifestations of Mercurial Diuretics in Man, J. A. M. A. **119**:1006-1011 (July 25) 1942.

14. Griffith, J. C.; Lindauer, M. A.; Roberts, E., and Rutherford, R. B.: Studies of Criteria for Classification of Arterial Hypertension: VI. Treatment with Thiocyanate, Am. Heart J. **21**:90-93 (Jan.) 1941. Robinson, R. W., and O'Hare, J. P.: Further Experiences with Potassium Sulfocyanate Therapy in Hypertension, New England J. Med. **221**:964-969 (Dec. 21) 1939.

15. Barker.[2f] Barker, Linberg and Wald.[11]

16. Page, I. H., and Corcoran, A. C.: Hypertension, in Steele, J. M., and others: Advances in Internal Medicine, New York, Interscience Publishers, Inc., 1942, p. 83.

has indicated that even with so-called therapeutic or even lower concentrations, serious intoxications may occur. Of the 3 fatal cases in which blood concentrations were determined it can be seen that in Garvin's the toxic symptoms appeared when the blood thiocyanate level had reached only 13.6 mg. per hundred cubic centimeters; that in Russell and Stahl's case it was between 15.2 and 21.7 mg., and, finally, that in our case, probably the most conspicuous of all, the blood level had reached only 7 mg. per hundred cubic centimeters when the intoxication began. It should be pointed out that the "important" blood concentrations on which the clinician must depend and on which the correct evaluation of the cases should be based are those obtained before or at the very onset of symptoms of toxicity and not the values obtained afterward. Thus in the 3 cases the cyanate level rose rather sharply during the course of the poisoning, possibly because of a sudden release of the stored drug from the injured tissues; but, at least in Garvin's case, it never reached the levels at which "serious toxicity" occurs, according to the experience of Barker and associates.

We feel, therefore, that the prevalent concepts regarding toxicity and mode of administration of thiocyanate should be partly modified. We favor now, with Crockett and Moench,[17] the use of smaller doses than those usually prescribed. Amounts of from 0.1 to 0.3 Gm. per day, depending on body weight, at the beginning and slowly increased afterward, the blood thiocyanate being carefully watched at the third and seventh day and thereafter at gradually increased intervals of one to four weeks, would appear convenient in our opinion.

Caviness and co-workers[18] advocated treatment with the lowest effective blood level of the drug possible; they rarely found it necessary to increase the level over 9 mg. per hundred cubic centimeters. Other authors also[19] have found good responses in a certain number of cases with blood concentrations as low as 3 to 6 mg. per hundred cubic centimeters. It is possibly a fact that somewhat better responses are obtained with higher levels, as those of 8 to 12 mg. as advocated by Barker, Linberg and Wald,[11] and, moreover, that some patients may respond only at these concentrations. We feel, nevertheless, that thiocyanate therapy should be restricted to patients who react with a decline of blood pressure on levels of from 2 to 5 mg. per hundred cubic centimeters, as, fortunately, the majority of patients in our experience have done, and that higher levels than these are potentially toxic and should not be attempted.

Special care should be given to the gradient of ascent of blood thiocyanates. Abrupt ascents were obtained in the 3 fatal cases in which determinations of blood level were done. Thus in Garvin's case the level rose to 3.8 mg. during the first five days and to 10 mg. on the eleventh day of treatment; in Russell and Stahl's case it rose to 4.2 mg. on the second day and to 15.2 mg. nine days later. In our case the level rose from 2.5 to 7 mg. in as short a span as seven days. It may be inferred from this that a too sharp increase in the blood thiocyanate content, perhaps around or over 0.75 mg. per day, possibly means either an excessive retention of the drug in the body or an excessive dose. In both instances the abrupt ascent observed may be the forerunner of much higher and potentially toxic blood levels if the dosage is not sharply reduced.

The presence of low blood thiocyanate before death in our patient, despite the high content of drug in the tissues at necropsy is in disagreement with observations made on human beings and on animals,[2a] which tend to demonstrate that the blood concentration of thiocyanate closely follows the concentration in the tissues. We have found no explanation for this; possibly in our case it was due to good urinary excretion of the drug and to the great power of retention of the tissues intoxicated with it.

CONCLUSIONS

In its struggle against disease medicine has created a certain number of therapeutic procedures that under some conditions may defeat the purpose for which they are administered, causing death. Such is the case with arsenical compounds for syphilis, sulfonamide compounds, digitalis, mercurial diuretics and others. After a long period of clinical and experimental observations and in view of the rather small number of deaths as compared with the imposing number of lives providentially saved, medical practice has come to justify their general use.

We are aware that authors with considerable experience and authority are enthusiastic advocates of the potassium thiocyanate therapy for

17. Crockett, K. A., and Moench, L. G.: Potassium Thiocyanate Treatment of Hypertension, J. A. M. A. **120**:982 (Nov. 21) 1942.

18. Caviness, V. S.; Umphlet, T. L.; Peasley, E. D.; Bell, T. A., and Satterfield, G. H.: Potassium Sulfocyanate in Treatment of Hypertension, North Carolina M. J. **2**:283 (June) 1943; abstracted, J. A. M. A. **117**: 1046 (Sept. 20) 1941.

19. Blaney, L. F.; Geiger, A. J., and Ernst, R. G.: Potassium Thiocyanate in the Treatment of Hypertension, Yale J. Biol. & Med. **13**:493-507 (March) 1941. Flexner, M.: Medical Treatment of Hypertension, South. M. J. **34**:917-921 (Sept.) 1941; cited by Page and Corcoran.[16]

hypertension, having never observed seriously untoward reactions. This merely shows that such reactions are fortunately rare, but by no means should it cause disregard for the accumulated data on thiocyanate toxicity that less fortunate workers have contributed. The empiric use of thiocyanates is at the present time undergoing the phase of study necessary for the correct appraisal of any drug. Up to the present time it is known only that this therapy is able to relieve two of the manifestations of hypertensive disease, namely the high blood pressure and the symptomatic complaints, but it is not known how this treatment modifies the course and the prognosis of the disease. Moreover, a comprehensive statistical study of the frequency with which severe intoxications occur is lacking. If these two points are not favorably answered by the future, this form of treatment should be abandoned. There would be no justification for the use of a substance that produces no real benefits in the disease for which it is administered, that is potentially toxic and that may even cause death.

SUMMARY

Another case, the seventh thus far reported, of death due to the therapeutic use of potassium thiocyanate for hypertension is added to the literature. A distinct fault in dosage on the part of the patient was responsible for the intoxication; it emphasizes the danger of prescribing the drug in easily inaccurately measured forms, like the solution for drop administration used for this case.

The thiocyanate concentration of the blood at the onset of toxic symptoms was only 7 mg. per hundred cubic centimeters. The concentrations of the drug in the tissue are the highest ones thus far reported in similar instances. A prominent feature of the postmortem examination was the finding of an acute necrotic nephrosis that had produced no symptoms or signs during life.

VENESECTION FOR THE PLETHORIC PATIENT

LAURENCE E. HINES, M.D., AND DONALD L. KESSLER, M.D.
CHICAGO

It is traditional to consider the well built, strong, plethoric, overweight person as a candidate for apoplexy or heart disease. Because of the lack of recorded observations to support this clinical impression, a study of the erythrocyte counts and hemoglobin contents of a series of proved cases of coronary thrombosis was made. A study of 58 cases in which there was either autopsy evidence or a series of electrocardiographic tracings typical of coronary thrombosis has revealed that only 8 per cent of the patients had an erythrocyte count of less than 4,500,000 per cubic millimeter and that only 11 per cent had a hemoglobin content of less than 13.0 Gm. There were 36 men, with a mean erythrocyte count of 5,090,000 per cubic millimeter, and 22 women, with a mean erythrocyte count of 4,850,000 per cubic millimeter. Six per cent of the men and 13.5 per cent of the women had an erythrocyte count of less than 4,500,000 per cubic millimeter.

TABLE 1.—*Erythrocyte Counts for Thirty-Six Men with Coronary Thrombosis*

Per Cent of Patients				
3	8	47	36	6
Red Blood Cells in Millions				
6.0+	6.0-5.5	5.5-5.0	5.0-4.5	4.5-
6.11	5.90	5.41	4.96	4.49
	5.85	5.41	4.93	4.42
	5.74	5.40	4.92	
		5.39	4.91	
		5.31	4.84	
		5.30	4.78	
		5.27	4.75	
		5.22	4.70	
Mean: 5.09		5.20	4.70	
		5.16	4.60	
		5.15	4.53	
		5.13	4.50	
		5.10		
		5.09		
		5.08		
		5.06		
		5.03		

A relation between the erythrocyte count and clotting tendency having been suggested, a clotting study on 15 persons was made. Eight plethoric patients with evidence of either coronary or cerebral thrombosis and 7 controls, including plethoric, normal and anemic persons, were studied. These included patients with polycythemia vera, obesity, leukemia, chronic glomerulonephritis and Hodgkin's disease, as well as normal controls.

Hemoglobin was studied by the Sahli method; prothrombin time, by Quick's method. For hematocrit determinations heparin was the anticoagulant. A simple test for sensitivity to heparin described by de Takats [1] was used in this study. Ten milligrams of purified heparin was injected intravenously. The coagulation time was determined before the injection and ten, twenty, thirty and forty minutes after the injection. A finger tip of each patient was punctured with a standard automatic lance. The first drop of blood was wiped off; the second was taken up in a chemically clean capillary tube 1.0 mm. in diameter, which was held in the hand during the determination for thermostatic control. The tube was broken every thirty seconds, and the appearance of the first thread of fibrin was taken as the end point,

TABLE 2.—*Erythrocyte Counts for Twenty-Two Women with Coronary Thrombosis*

Per Cent of Patients				
0	9	65	13½	13½
Red Blood Cells in Millions				
6.0	6.0-5.5	5.5-5.0	5.0-4.5	4.5-
....	5.97	5.40	4.93	4.39
	5.90	5.05	4.92	3.73
		4.90	4.90	3.44
		4.80		
		4.80		
		4.85		
		4.80		
Mean: 4.85		4.74		
		4.71		
		4.71		
		4.70		
		4.69		
		4.55		
		4.54		

From the departments of Medicine, Northwestern University Medical School and St. Joseph Hospital.

1. de Takáts, G.: Surg., Gynec. & Obst. **77**:32-36, 1943.

measured from the time the second drop of blood appeared. The curves thus obtained were classified as showing hyporeaction if the coagulation time beginning ten minutes after the injection was four and a half minutes or less and hyperreaction if the coagulation time was over seven and a half minutes.

The results are shown in chart 1. In this chart the prothrombin time in percentage of normal and the reaction time to heparin (ten minutes) represents the clotting activity. When these factors are plotted against the erythrocyte counts, arranged serially from low to high, a definite increase of the clotting activity is seen to occur as the erythrocyte count increases.

TABLE 3.—*Hemoglobin Values for Fifty-Eight Patients with Coronary Thrombosis*

Per Cent of Patients				
36	3	30	20	11
Hemoglobin in Grams				
16.0	16.0-15.0	15.0-14.0	14.0-13.0	13.0-
15.2	15.2	14.8	13.4	12.6
15.0	15.1	14.5	13.4	12.5
15.0		14.5	13.3	12.0
17.5		14.5	13.3	11.9
17.4		14.5	13.2	11.8
17.3		14.5	13.2	8.8
17.0		14.5	13.2	
17.0		14.5	13.2	
16.8		14.5	13.2	
16.4		14.4	13.2	
16.4		14.3	13.1	
16.2		14.1		
16.1		14.0		
16.0		14.0	Mean: 14.5	
16.0		14.0		
16.0		14.0		
16.0		14.0		
16.0				
16.0				
16.0				

This correlation, although not exact in the individual case, shows a definite trend in the group, more pronounced in the plethoric persons than in the normal and anemic controls. De Takats has previously demonstrated that the response to heparin in patients with thrombosis is reduced. In this series, there is a high incidence of hyporeaction in the plethoric person without clinical evidence of thrombosis, and the erythrocyte count is uniformly elevated or in the upper limits of normal. The presence of a high erythrocyte count, a flat heparin tolerance curve or a short prothrombin time cannot be considered in itself to be a factor capable of precipitating thrombosis, but the presence of all three in a group of persons with a known tendency to thrombosis appears to provide more susceptibility once thrombus formation has been initiated.

A study was then made of 3 patients with flat heparin tolerance curves to determine the effect of bleeding on the clotting mechanism. It was formerly believed that venesection provoked erythropoietic stimulation. However, it has been shown by Falconer,[2] Stephens and Kaltreider,[3] Holbrook,[4] Hines and Darnall [5] and others that

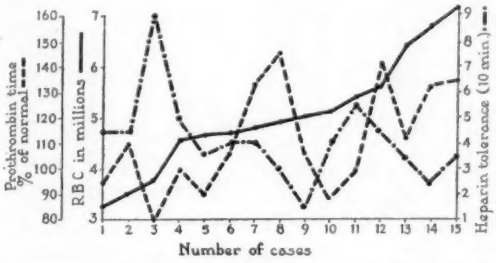

Chart 1.—Fifteen cases. The erythrocyte count is plotted serially from low to high. The clotting index is plotted from the prothrombin time (in percentage of normal) and the reaction to heparin taken ten minutes after its injection.

small (100 to 500 cc.) frequent bleedings in patients with polycythemia vera controlled the symptoms and lowered the erythrocyte, hemoglobin and hematocrit values without producing a significant rise in the reticulocyte count. Three patients were studied: a normal control, a patient with polycythemia vera and a patient with

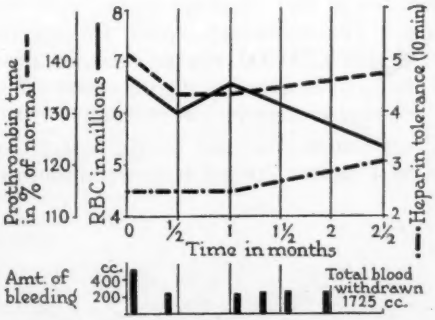

Chart 2.—Results of bleedings in a patient with polycythemia vera.

a recent coronary thrombosis. The patient with polycythemia vera was studied before, during and after a series of small bleedings. A total

2. Falconer, E. H.: Ann. Int. Med. **7**:172-189, 1933.

3. Stephens, D. J., and Kaltreider, N. L.: Ann. Int. Med. **10**:1565-1581, 1937.

4. Holbrook, A. A.: Wisconsin M. J. **40**:899-910, 1941.

5. Hines, L. E., and Darnall, W. C.: Am. J. M. Sc. **206**:434-438, 1943.

of 1,725 cc. of blood was withdrawn in six bleedings over a period of two months. During this period the erythrocyte count decreased from 6,600,000 to 5,290,000 cells per cubic millimeter; the prothrombin time was slightly increased, and the response to heparin was slightly increased. From another plethoric patient with recent coronary thrombosis, auricular fibrillation and obesity, 800 cc. of blood was withdrawn

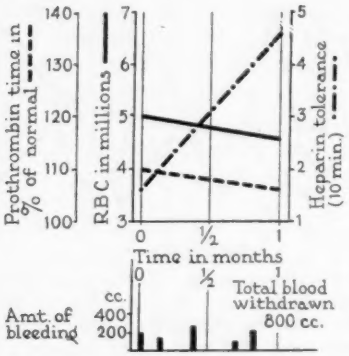

Chart 3.—Results of bleedings in a patient with a recent coronary thrombosis.

in five bleedings in one and a half months. The erythrocyte count dropped from 5,000,000 to 4,500,000 cells per cubic millimeter; the prothrombin time was slightly increased, and the response to heparin was noticeably increased. From a normal patient 1,350 cc. of blood was withdrawn in four bleedings during a six week period. The erythrocyte count dropped from 5,400,000 to 4,290,000 cells per cubic millimeter; the prothrombin time was slightly shortened, and the response to heparin was reduced.

These studies show that small frequent bleedings in 1 patient (recent coronary thrombosis) produced a lessening of the clotting tendency, as evidenced by an increase in the prothrombin time and an elevation in the heparin tolerance. The same results were obtained in the patient with polycythemia vera, in which the tendency to thrombosis is well known. In contrast, the normal control showed no change in the prothrombin time, although the response to heparin was greatly diminished.

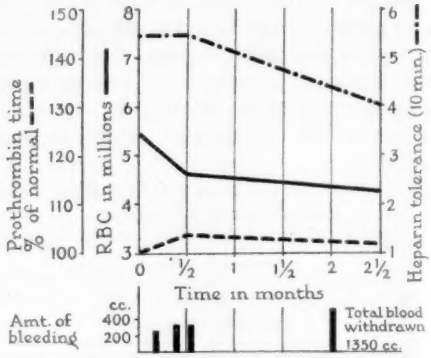

Chart 4.—Results of bleedings in a normal person.

SUMMARY

Only 2 of 58 patients proved to have had coronary thrombosis had an erythrocyte count of less than 4,000,000. Diminished clotting time after administration of heparin and a shortened prothrombin time were the common findings for patients with high erythrocyte counts.

Similar changes in the clotting mechanism have been observed in patients known to have thrombosis. These facts suggest that the use of venesection both for preventing and for treating thrombosis is rational. The changes produced by bleeding a small number of patients seem to support the idea.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JULY 1943 TO JUNE 1944

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AND
WILLIAM E. RICKETTS, M.D.
CHICAGO

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From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

INTRODUCTION

The publications dealing with gastroenterologic subjects reveal continued progress through the year, with no startling developments. The new chemotherapeutic agents, the sulfonamide compounds and penicillin, have proved perhaps least helpful in infections of the digestive tract.

Several excellent books have appeared, none of which can be reviewed in detail. Two of the three volumes of "Gastroenterology," written by Bockus,[1] have been printed and can be highly recommended. The second edition of "Diseases of the Digestive System," edited by Portis[2] is likewise excellent. Babkin[3] has published an exhaustive treatise on the digestive glands. Rehfuss[4] has written a commendable book on "Indigestion; Its Diagnosis and Management, with Special Reference to Diet." Templeton's[5] "X-Ray Examination of the Stomach" is a splendid monograph on the roentgenologic examination of the upper part of the digestive tract. Hodges'[6] book presents an up-to-date and practical consideration of roentgenologic gastroenterology. Dack's[7] monograph on "Food Poisoning" is a classic. The second edition of Manson-Bahr's[8] "Dysenteric Disorders" is an excellent reference text, as is the third edition of "Clinical Parasitology" by Craig and Faust.[9] Bargen,[10] chiefly on the basis of his own enormous experience with nonspecific ulcerative colitis, has written a splended monograph on the "Modern Management of Colitis." Several review articles have appeared, such as those on roentgenology by Rigos and Kirklin,[11] on diseases of the colon by Wollaeger and Bargen[12] and on tropical disease by Faust,[13] as well as Faust's[14] review of amebiasis in his Alvarenga Prize Lecture. Bethell and associates[15] have reviewed the literature dealing with the relationship between gastritis, pernicious anemia and gastric neoplasm, and Reimann[16] has reviewed that pertaining to intestinal infections.

1. Bockus, H. L.: Gastroenterology, Philadelphia, W. B. Saunders Company, 1943, vol. 1; 1944, vol. 2.

2. Portis, S. A.: Diseases of the Digestive System, ed. 2, Philadelphia, Lea & Febiger, 1944.

3. Babkin, B. P.: Secretory Mechanism of the Digestive Glands, New York, Paul B. Hoeber, Inc., 1944.

4. Rehfuss, M. E.: Indigestion: Its Diagnosis and Management, Philadelphia, W. B. Saunders Company, 1943.

5. Templeton, F. E.: X-Ray Examination of the Stomach, Chicago, University of Chicago Press, 1944.

6. Hodges, F.: The Gastro-Intestinal Tract: A Handbook of Roentgen Diagnosis, Chicago, The Year Book Publishers, Inc., 1944.

7. Dack, G. M.: Food Poisoning, Chicago, University of Chicago Press, 1943.

8. Manson-Bahr, P.: The Dysenteric Disorders, ed. 2, Baltimore, Williams & Wilkins Company, 1943.

9. Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 3, Philadelphia, Lea & Febiger, 1943.

10. Bargen, J. A.: The Modern Management of Colitis, Springfield, Ill., Charles C Thomas, Publisher, 1943.

11. Rigos, F., and Kirklin, B. R.: Diagnostic Roentgenology in Gastroenterology for the Year 1941, Gastroenterology **1**:669-686 and 942-960, 1943.

12. Wollaeger, E. E., and Bargen, J. A.: The Large Intestine: A Review of Current Literature, Gastroenterology **2**:102-120, 1944.

13. Faust, E. C.: Diseases in Tropical Zones, Gastroenterology **1**:995-1012, 1943.

14. Faust, E. C.: Some Modern Conceptions of Amebiasis, Science **99**:45-51 and 69-72, 1944.

15. Bethell, F. H.; Sturgis, C. C.; Mallery, O. T., Jr., and Rundles, R. W.: Blood: A Review of the Recent Literature, Arch. Int. Med. **74**:37-39 (July) 1944.

16. Reimann, H. A.: Infectious Diseases: Tenth Annual Review of Significant Publications, Arch. Int. Med. **74**:287-291 (Oct.) 1944.

ESOPHAGUS

Motility.—McLaren[17] studied kymographically the movement of food down the esophagus and found that a wave of contraction moves at an average speed of 3 inches (7.5 cm.) in two seconds. The wave, increasing in length as it progresses, appears to push the food along without a preceding wave of relaxation.

Esophageal Pain.—Moersch and Miller,[18] in an excellent review of esophageal pain, comment on the scarcity of knowledge concerning the innervation of the esophagus and the uncertainty regarding the pathway for the conduction of pain. Experimentally and clinically, the mechanism of pain seems to consist chiefly in stretching of the esophagus with resultant increase in the tension. The pain is much more likely to occur with acute ulceration, inflammation and presumably associated spasm than with slow-growing lesions, such as carcinoma. There are wide variations among individuals as regards susceptibility to and the radiation of esophageal pain. The great difficulty in distinguishing at times between angina pectoris and the pain of hiatus hernia is emphasized.

17. McLaren, J. W.: Kymography and Its Application to Esophageal Movement, Brit. J. Radiol. **16**: 270-273, 1943.

18. Moersch, H. J., and Miller, J. R.: Esophageal Pain, Gastroenterology **1**:821-831, 1943.

Atresia.—Singleton and Knight [19] report 4 cases of congenital atresia of the esophagus with tracheoesophageal fistulas. Three of the patients died, 1 after gastrostomy, 1 after a posterior extrapleural operation in which the fistula was ligated and the third after a transpleural operation in which the fistula was ligated and an esophageal anastomosis made. In the fourth case a gastrostomy was done, after which through a transpleural approach the fistula was ligated with an end to end anastomosis of the esophagus.

The child lived seven months. The advantages of the transpleural approach are enumerated. Ladd [20] discussed the different types of tracheoesophageal fistulas and esophageal atresia. Since 1939, 34 patients have been operated on with his method, 6 with primary anastomosis of the esophagus, 2 surviving; 28 had the three stage operation consisting of obliteration of the esophageal fistula, gastrostomy and esophagostomy, 9 surviving. The primary anastomosis of the esophagus is considered the procedure of choice when the ends of the esophagus can be approximated. Humphreys [21] reviews the 134 cases published in the literature and includes 19 of his own in which operation was performed for congenital atresia of the esophagus. Twenty-four babies have survived operation and are still living today. A direct anastomosis was successful in 8; in 16 the fistula was divided in the mediastinum, the upper segment being brought out in the neck and a gastrostomy made for feeding purposes. Royer [22] reports the case of a 7 year old boy with a congenital stenosis of the esophagus of the canalicular type treated successfully by means of progressive dilation of the esophagus.

Esophagitis.—Brown [23] placed a group of 17 white rats between 2 and 3 months of age on a diet of Texas rice with cottonseed oil in the ratio of 20 cc. of oil and 1,000 Gm. of rice and a slice of fresh carrot for a period of six months. No consistent abnormality was noted in any organs other than the esophagus. Seven rats had ulcers in the lower part of the esophagus and 1 an ulcer of the forestomach. Hyperkeratosis and various stages of inflammation, muscular atrophy and fibrosis were noted. Such lesions were rarely found in a control group.

Paul [24] describes 5 cases of esophagitis resulting in stricture formation. In 1 it followed the use of a negative pressure tube for a week and was relieved by numerous esophageal dilation. In 1 case it was associated with a congenitally short esophagus with an esophageal hiatus hernia. In 1 case there was an esophageal stricture associated with a ruptured peptic ulcer. In another case the stricture was associated with an ulcer of the lesser curvature of the stomach. In the fifth case it developed over a period of three years and was accompanied with diffuse intermittent spasm of the lower half of the esophagus. Paul emphasizes the probable role of acid gastric juice in the production of the esophageal ulceration. The roentgenologic changes consist of the severe spasm of the distal part of the esophagus, loss of mucosal folds and a fine roughening of the surfaces. If the lesion is present for a sufficient length of time, the roentgen findings may be those of a diffuse fibrous stricture. In some cases of chronic esophagitis the most striking roentgenologic manifestation is intermittent diffuse spasm of the lower half or third with thickening of the mucosal folds. The appearance is much different from "curling of the esophagus."

Ulcer.—Cleaver,[25] in a well documented and well illustrated presentation of 10 cases of peptic ulceration of the esophagus, describes the definite clinical and radiologic manifestations and the quite constant association with a congenital short esophagus or a diaphragmatic hernia, permitting regurgitation of acid contents from the stomach into the esophagus. Similarly, ectopic gastric mucosa in the esophagus can produce chronic ulceration, as shown by biopsy in 2 cases and in a third reported by Bonorino Udaondo, d'Alotto and Nasio.[26] Peptic ulceration was associated with a short esophagus in all the cases observed by Johnstone.[27] Congenital shortening might account for ulceration in children. However, the frequent occurrence in old age is ascribed to loss of elasticity of tissue in the aged, with re-

19. Singleton, A. O., and Knight, M. D.: Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula, Ann. Surg. **119**:556-572, 1944.

20. Ladd, W. E.: The Surgical Treatment of Esophageal Atresia and Tracheoesophageal Fistulas, New England J. Med. **230**:625-637, 1944.

21. Humphreys, G. H.: The Surgical Treatment of Congenital Atresia of the Esophagus, Surgery **15**:801-823, 1944.

22. Royer, M.: Estenosis congenita canalicular del esofago, curacion con la dilatacion, Arch. argent. de enferm. d. ap. digest. y de la nutrición **18**:697-703, 1943.

23. Brown, C. E.: Dietary Ulcers of the Esophagus of the Rat, Am. J. Path. **19**:785-796, 1943.

24. Paul, L. W.: Roentgenologic Aspects of Acute and Chronic Esophagitis, Radiology **41**:421-430, 1943.

25. Cleaver, E. E.: Chronic Peptic Ulceration of the Oesophagus, Am. J. Digest. Dis. **10**:319-329, 1943.

26. Bonorino Udaondo, C.; d'Alotto, V., and Nasio, J.: Ulcera péptica del esófago, Prensa méd. argent. **29**:1342-1347, 1943.

27. Johnstone, A. S.: Peptic Ulceration of the Oesophagus with Partial Thoracic Stomach, Brit. Radiol. **16**:357-361, 1943.

sultant shortening of the esophagus and laxity of the hiatus. Increased abdominal pressure may cause a small portion of the stomach to slip freely through the hiatus, forming a reducible thoracic portion of the stomach. The laxity of the hiatus permits regurgitation of gastric juice. The diagnosis of peptic ulceration and partial thoracic stomach is essentially roentgenologic, the important feature being the demonstration of both esophageal and gastric mucosa above the diaphragm. With ulceration there may be narrowing due to spasm at the junction of esophagus and stomach.

Mediastinitis.—Hawes [28] reports that roentgenologic examination of the barium-filled esophagus is a definite aid in the differentiation of mediastinal infection and tumor. As observed in 5 cases of active mediastinal tuberculosis, the appearance of the esophagus is changed by pressure, by adhesions and by actual involvement of the mucosal surface. The presence of adhesions is indicated in the roentgenogram by a number of projections, appearing either as points or rounded waves, in the involved segment of the esophagus. These projections are constant and probably are produced by traction.

Mascheroni, Reussi and Lafage [29] describe a 49 year old man with spasm of the lower part of the esophagus in whom after esophagoscopy a transitory esophagomediastinal fistula and abscess of the lung developed. Recovery occurred gradually with the administration of 0.5 Gm. of sulfathiazole every three hours for twenty-eight days. Grace and Irwin [30] report perforation of the cervical portion of the esophagus by a plastic denture resulting in mediastinitis, treated by surgical drainage, with recovery and no evidence of esophageal obstruction.

Scleroderma.—Hale and Schatzki [31] studied 22 patients with scleroderma. In 5 of 7 patients complaining of dysphagia the esophagus was abnormal; similar abnormalities were also found in 8 patients without symptoms. The abnormalities consisted mainly in delayed emptying combined with a decrease in peristalsis in the lower half of the esophagus. There was no gross dilatation as in cardiospasm. Barium sulfate passed into the stomach in a slow but constant trickle. There was a tendency for the esophagus to remain open after the main bolus had passed, to contain a large amount of air and to be outlined by barium abnormally adherent to the wall.

Varices.—Welt and Blatteis [32] report massive hemorrhage from esophageal varices attributed to portal obstruction resulting from scar tissue formation following multiple hepatic abscesses secondary to appendical peritonitis. The patient was treated successfully during a period of bleeding by injection of the sclerosing solution into the esophageal veins. Duffy and Fraser [33] report another instance of fatal bleeding from esophageal varicosities with splenomegaly of unknown cause and a normal liver at autopsy.

Cardiospasm.—Weiss [34] considers cardiospasm as an organ neurosis, a form of conversion hysteria deeply rooted in the unconscious mental life of the individual. It arises coincident with an emotional conflict in a person whose early life gives evidence of personality difficulties. Exacerbations frequently can be correlated with fresh psychic insults touching the particular complex of the individual. Psychosomatic observations in 9 cases are reported.

Roentgenologically the elongated tortuous and kinked esophagus may be seen to encroach on the pulmonary fields, but it is easily distinguished roentgenologically even though there is seldom a fluid level.[35] The shadow is relatively opaque and may be mistaken for other types of mediastinal enlargements. D'Silva [36] describes a dilated esophagus discovered on routine examination of the chest and differing from the usual cases by the absence of symptoms and of evident spasm and by the abnormal shape and length of the esophagus. Hurst [37] reports on 9 patients with respiratory symptoms resulting from pressure of the distended esophagus or from aspiration of regurgitated food. In 1 patient the condition was mistaken for a mediastinal tumor; in 1 pleural effusion developed secondary to aspira-

28. Hawes, L. E.: The Roentgenological Changes in the Esophagus in Tuberculous Mediastinitis, Am. J. Roentgenol. **5**:575-584, 1944.

29. Mascheroni, H. A.; Reussi, C., and Lafage, L. A.: Fistula esófagicomediastinica post-esofagoscopia; absceso de pulmon; curación, Arch. argent. de enferm. d. ap. digest. y de la nutrición **18**:712-722, 1943.

30. Grace, K. D., and Irwin, T. M.: Perforation of the Cervical Esophagus with Mediastinitis, Surgery **14**:631-639, 1943.

31. Hale, C. H., and Schatzki, R.: The Roentgenological Appearance of the Gastro-Intestinal Tract in Scleroderma, Am. J. Roentgenol. **51**:407-420, 1944.

32. Welt, B., and Blatteis, S. R.: Esophageal Varices: Case Report, Am. J. Surg. **63**:415-417, 1944.

33. Duffy, D. G., and Fraser, A. N.: Fatal Bleeding from Esophageal Variocosities, M. J. Australia **1**: 202-204, 1944.

34. Weiss, E.: Cardiospasm: A Psychosomatic Disorder, Psychosom. Med. **6**:58-70, 1944.

35. Williams, E. R.: Dilatation of the Esophagus, Brit. J. Radiol. **16**:220, 1943.

36. D'Silva, J. L.: Symptomless Enlargement of the Oesophagus, Brit. M. J. **1**:750-751, 1944.

37. Hurst, A.: Respiratory Complications of Achalasia of the Cardia with Mega-Oesophagus, Guy's Hosp. Rep. **92**:68-73, 1943.

tion pneumonia, and 2 had paroxysmal coughing from regurgitation of food. In the case of the tenth sudden death resulted from asphyxia produced by obstruction of the glottis with regurgitated food.

Vines and Olsen [38] describe a 50 year old man with cardiospasm who had the typical picture of pellagra and was cured by nicotinic acid amide. The rarity of deficiency disease in patients with esophageal lesions is attributed to the fact that it seems less likely to develop in persons with partial starvation than among persons with poorly balanced diets.

Bersack,[39] in 227 patients with esophageal carcinoma, found 1 with associated achalasia of the cardia. Since dilatation of the cardia may delay the appearance of obstructive symptoms, frequent esophagoscopies are recommended for such patients. Bonorino Pero and Coppola [40] report the well documented and illustrated case of a 38 year old woman with megaesophagus for twenty-three years in whom a carcinoma of the middle of the esophagus finally developed.

Lichstein [41] describes a 50 year old white woman with an enormous tortuous esophagus due to cardiospasm for whom medical treatment over a period of three years availed little. Esophagogastrostomy was performed successfully, with almost complete symptomatic relief in spite of the fact that the new stoma did not seem to function well, as seen roentgenologically. This discrepancy between symptomatic relief and the behavior of the new cardia evident by roentgenologic examination has been noted by others following surgical treatment of this type and, indeed, is well known to exist after medical treatment, i. e., mechanical dilation of the cardia. Esophagogastrostomy is considered the treatment of choice for patients with cardiospasm not responding satisfactorily to dilatation.

Carcinoma.—Fleming,[42] in studying 42 cases of carcinoma of the esophagus, found that when the linear involvement exceeded 5 cm. there was a material increase in the metastases, suggesting a rough relationship between the size of the lesion and the extent of the spread. There was a high incidence of metastases to the liver. Since the majority of these lesions are squamous cell epitheliomas and such tumors elsewhere respond to irradiation therapy, Fleming suggests that such therapy might be more effective if a wider and shorter field of radiation were used rather than the usual long, narrow field. Smithers,[43] on the other hand, prefers the long narrow fields using six portals, one anterior, one posterior and four oblique. Although there have been no startling results, the relief of symptoms has been very much worth while and palliation can be obtained in many cases.

The most significant progress in esophageal disease has been made in recent years in the surgical treatment of carcinoma, intractable cardiospasm and stricture. Reports of successful transthoracic operations with or without resection of portions of the esophagus and, if indicated, of the stomach also have now come from many countries.[44]

STOMACH

Anorexia Nervosa.—Oppenheimer [46] illustrates the resemblance in the clinical picture of Simmonds' disease to anorexia nervosa; low basal metabolic rate, low blood sugar level, long duration of the symptoms, no relief from psychotherapy and yet at autopsy no abnormalities of the pituitary. Oppenheimer considers this an instance of "pseudo Simmonds's disease," 14 similar cases being reported in the literature.

38. Vines, R. W., and Olsen, A. M.: Cardiospasm with Associated Pellagra: Report of Case, Proc. Staff Meet., Mayo Clin. **18**:389-395, 1943.

39. Bersack, S. R.: Carcinoma of the Esophagus in Association with Achalasia of the Cardia, Radiology **42**:220-223, 1944.

40. Bonorino Pero, C., and Coppola, J. A.: El cáncer como complicación del megaesófago, Prensa méd. argent. **30**:2136-2140, 1943.

41. Lichstein, J.: Cardiospasm: Successful Treatment by Esophagogastrostomy, Am. J. Digest. Dis. **10**:271-275, 1943.

42. Fleming, J. A. C.: Carcinoma of the Thoracic Esophagus: Some Notes on Its Pathology and Spread in Relation to Treatment, Brit. J. Radiol. **16**:212-216, 1943.

43. Smithers, W. D.: The X-Ray Treatment of Carcinoma of the Esophagus, Brit. J. Radiol. **16**:317-322, 1943.

44. (*a*) Ferrari, R. C.: El tratamiento quirúrgico de las enfermedades del esófago, Arch. argent. de enferm. d. ap. digest. y de la nutrición **18**:651-696, 1943. (*b*) Clagett, O. T., and Wiig, L. M.: Transthoracic Resection of Esophagus and Stomach for Carcinoma: Report of Two Cases, Proc. Staff Meet., Mayo Clin. **18**:337-344, 1943. (*c*) Steele, G. H.: Carcinoma of the Oesophagus, Lancet **2**:797-798, 1943. (*d*) Resano, J. H.: Cancer del esófago recección y anastomosis (los exitos operatorios), Arch. argent. de enferm. d. ap. digest. y de la nutrición **19**:119-134, 1944. (*e*) Yurasov, E. E.: Reconstruction of Esophagus, Am. Rev. Soviet Med. **1**:206, 1944. (*f*) Brea, M. M.: Tratamiento quirúrgico del cáncer del esófago torácico, Medicina, Buenos Aires **4**:74-86, 1943. (*g*) Señorans, A. J.: Consideraciones sobre patologia del esófago, Arch. argent. de enferm. d. ap. digest y de la nutrición **18**:557-579, 1943. (*h*) Gotta, G.: Radiologia del esófago, ibid. **18**:580-607, 1943. (*i*) Brachetto-Brian, D.: Patologia del esófago, ibid. **18**:608-650, 1943.

45. Footnote omitted.

46. Oppenheimer, B. S.: Simmonds' Disease Versus Anorexia Nervosa: A Report of a Case with Necropsy Findings, J. Mt. Sinai Hosp. **10**:640-650, 1944.

Pernicious Vomiting of Pregnancy.—For thirty years Sir Arthur Hurst [47] has been convinced that the so-called pernicious vomiting of pregnancy is always hysterical. Fifty or 60 deaths from it are registered in England annually. Most modern textbooks discuss the differentiation between the toxic and the nervous form of pernicious vomiting of pregnancy. Gibberd teaches that in the rare cases in which Korsakoff's syndrome of peripheral neuritis with mental symptoms develops the vomiting is toxic in origin because of the resemblance of the clinical and pathologic conditions to those produced by alcohol. Hurst contends that these are rarely the results of the associated vitamin D deficiency and that there is no qualitative difference between the two types. A woman of 32 with continued vomiting, a pulse rate of 136 and pronounced emaciation was told by her father that she would have a bad time in pregnancy, as her mother had vomited all the time that she was pregnant. Hurst explained to her that there was no good reason why she must vomit after the first six weeks, in which vomiting is normal, and that her father's suggestion was all that was needed to lead to her present condition. In ten minutes he convinced her that she would not vomit again. Later he returned and watched her eat buttered toast and tea, which she had chosen for her first meal. There was no inclination to vomit then or at the following supper, but she did vomit the next morning. She was then transferred to a better psychologic environment and had no further trouble. Eleven months after delivery she again became pregnant and at once began to vomit so severely that her physician discussed termination of the pregnancy. The vomiting again yielded to psychologic treatment. Hurst thinks that toxemic vomiting of pregnancy, apart from that associated with eclampsia or acute hepatic necrosis, does not occur. Jaundice, however, may result from hysterical vomiting and disappears rapidly with an adequate diet.

Diaphragmatic Hernia.—Bremer [48] studied the embryonic development of the diaphragm and the different types of diaphragmatic hernia. Murphy and Hay,[49] in an excellent study of 72 patients with hiatus hernia, found anemia of different degrees, usually of the hypochromic type, in 70 per cent.

Symptoms, according to Turner,[50] may be absent or they may be varied, but they consist typically in anginoid pain, worse after meals, aggravated by the horizontal position and frequently accentuated by emotional stress. Distention of the lower third of the esophagus has been shown to produce anginoid pain, pyrosis and heartburn. In the roentgenologic demonstration of hernia, the Muller maneuver is of value. Interference with the vascular supply of the herniated stomach may cause congestion of the mucosa, gastritis and even peptic ulceration. The formation of fibrous adhesions to the left dome of the diaphragm may cause pronounced local circulatory embarrassment and even pain in the left shoulder. Hiatus herniation was found on 3.5 per cent of 1,500 examinations of the upper part of the gastrointestinal tract. Hernias are more easily visualized in a slight Trendelenburg position. The demonstration of gastric rugae traversing the hiatus suffices for a positive diagnosis. Persistently prominent rugal folds suggest vascular interference in the hernia. A broadly dilated esophageal hiatus with a mobile and distensible herniated portion of the stomach and a normal rugal pattern is least often connected with symptoms. Conversely, a portion of stomach persistently herniated at the hiatus with no mobility, limited distensibility and decided prominence of rugal pattern is most likely directly productive of symptoms.

Of the many complications coincidental to hiatus hernia, total volvulus of the stomach is one of the rarest and most serious. A left diaphragmatic hernia was reported [51] with attacks of pressure, apparently induced as a result of conscious or subconscious emotional reactions and relieved by spontaneous or induced belching or vomiting. Volvulus of the distal half of the stomach finally resulted, with rotation anteriorly and upwards. The subsequent incarceration of the antrum in the left hernial sac with complete kinking of the antrum produced total acute gastric obstruction. A method of obliterating the hernial sac by tamponade was employed with apparently good results.

Gastric Motility.—Van Liere and Northup [52] found that the addition of 500 cc. of tap water

47. Hurst, A., cited, Hysterical Nature of the So-Called Pernicious Vomiting of Pregnancy, Foreign Letters (London), J. A. M. A. **125**:223 (May 20) 1944.

48. Bremer, J. L.: The Diaphragm and Diaphragmatic Hernia, Arch. Path. **36**:539-549 (Dec.) 1943.

49. Murphy, W. P., and Hay, W. E.: Symptoms and Incidence of Anemia in Hernia at the Esophageal Hiatus, Arch. Int. Med. **72**:58-68 (July) 1943.

50. Turner, J. W.: Gastric Herniation at the Esophageal Hiatus, Am. J. Roentgenol. **50**:33-41, 1943.

51. Vorhaus, M. G., and Stetten, DeW.: Volvulus and Incarceration of Stomach in a Diaphragmatic Hernia with Complete Acute Gastric Obstruction, Gastroenterology **2**:307-315, 1944.

52. Van Liere, E. J., and Northup, D. W.: The Effect of Water Taken with Meals on Gastric Emptying, Gastroenterology **2**:195-200, 1944.

to a standard 200 cc. test meal exerted no appreciable effect on the gastric emptying time nor did the addition of 1,000 cc. of water except in 1 instance.

Significant prolongation in gastric emptying time was observed by Jacobson and Palmer [53] in patients whose peripheral erythrocyte count was below 1,500,000. Contrary to the general belief that gastrointestinal motility is increased and the passage of material from the stomach and through the intestinal tract accelerated in pernicious anemia, these functions were found to be normal or delayed. Achlorhydria per se does not significantly affect the rate of gastric emptying.

A study made by Henschel, Taylor and Keys [54] of the decreased appetite frequently observed in hot weather disclosed that the emptying time is actually faster at the higher temperatures. Twelve of the subjects had an average decrease of 30 per cent. Observations on about 100 normal men doing hard work at 120 F. failed to indicate any lack of appetite or any signs of decreased gastric activity except in actual heat exhaustion.

Extracts of the urine of patients with duodenal ulcer and of normal human males administered intravenously inhibit the gastric motility of dogs with gastric fistula, the amount required being three to five times that needed to depress gastric secretion.[55] The motility-inhibiting factor apears to be distinct from the ulcer prevention and healing factor.

Hoelzel [56] subjected himself to a thirty-three and a forty-one day fast in order to study the effect on gastric activity of starvation and realimentation with various types of foodstuffs. The results are interpreted as being in accord with the author's previous observations on the importance of proteins. The role of subjective factors in such work is difficult for us, the reviewers, to appraise.

Twenty-five experiments measuring changes in gastric motor activity occurring before and during nausea produced by a variety of stimuli were carried out by Wolf [57] on 4 human subjects. The earliest change noted was a cessation of gastric contraction with a decrease in tone. Prolonged or increased stimulation would result in nausea, sweating, pallor of the face and gastric mucosa and tachycardia. When neostigmine hydrobromide, 0.015 Gm., and atropine sulfate, 0.012 Gm., were given, vigorous gastric contractions were produced that persisted in spite of stimuli that produced vertigo and nystagmus and had previously produced cessation of gastric motility. Nausea did not occur. No predictable effect was produced when neostigmine or atropine was given alone. Nausea occurred only during phases of inhibited gastric motility.

Airsickness, seasickness, trainsickness and sickness produced by amusement parks are all characterized by symptoms related to the gastrointestinal tract. Motion sickness was produced experimentally in 100 subjects undergoing testing for a twenty minute period.[58] Fluoroscopic studies were made of the gastric tone, the gastric peristalsis, the correlation between peristalsis and gastric tone, pylorospasm, intestinal progress and intestinal pattern. Two groups were separated: 28 per cent that became sick and 72 per cent that were immune. No specific type of gastrointestinal tract from either an anatomic or a functional standpoint was associated with susceptibility to motion sickness. A definite decrease in gastric tone and in peristalsis occurred after the motion test in a significant number of subjects. Changes in gastric tone and in peristalsis showed a statistically significant positive correlation.

A review [59] of 86 papers pertaining to the action of atropine on the gastrointestinal tract disclosed that while much is known there is real need for clarification of the movements of the intestines and their response to drugs.

Experiments on a series of 9 trained dogs indicate that emotional stress as obtained by stimulation of a variety of somatovisceral and viscerovisceral reflexes does not result in polyrospasm, as is the prevalent opinion, but rather in an inhibition of the entire pyloric sphincter region (antrum, sphincter and bulb). Greater

53. Jacobson, L. O., and Palmer, W. L.: The Effect of Anemia on Gastric Emptying, Gastroenterology **1**: 1133-1140, 1943.

54. Henschel, A.; Taylor, H. L., and Keys, A.: The Gastric Emptying Time of Man at High and Normal Environmental Temperatures, Am. J. Physiol. **141**:205-208, 1944.

55. Bourque, J. E., Jr.; Friedman, M. H. F.; Patterson, T., and Sandweiss, D. J.: The Effect of Intravenous Injections of Urine Extracts an Gastric Motility, Gastroenterology **1**:1049-1054, 1943.

56. Hoelzel, F.: An Explanation of Appetite, Am. J. Digest. Dis. **11**:101-108, 1944.

57. Wolf, S.: The Relation of Gastric Function to Nausea in Man, J. Clin. Investigation **22**:877-882, 1943.

58. McDonough, F. E., and Schneider, M.: The Effect of Motion on the Roentgenographic Appearance of the Stomach and Small Bowel, Gastroenterology **2**: 32-45, 1944.

59. Henderson, V. E., and Sweeten, M. O.: The Effect of Atropine on the Gastro-Intestinal Canal and Its Glands, Am. J. Digest. Dis. **10**:241-247, 1943.

stimulation was required to produce inhibition after supradiaphragmatic vagotomy.[60]

Functional postoperative vomiting and periodic vomiting are attributed to spasm of the pylorus because the abdomen remains silent as long as the vomiting continues and peristaltic sounds recur within half an hour after the first administration of phenobarbital (luminal).[61]

Gastric Secretion.—The volume of the gastric content was greatly decreased by both atropine sulfate and morphine sulfate, was unaffected by the sodium salt of dehydrocholic acid and was increased both by pilocarpine hydrochloride and neostigmine methylsulfate. The volume of the duodenal contents aspirated simultaneously was decreased by atropine sulfate and morphine sulfate, was practically unchanged by pilocarpine hydrochloride and was increased by neostigmine methylsulfate, the sodium salt of dehydrocholic acid and secretin. Atropine sulfate reduced the amount of acid secreted and entering the duodenum and the buffering value of the duodenal contents, but its action on the secretion of acid was apparently greater than its action on the secretion of bile, the secretion of pancreatic juice and the secretion of the duodenal mucosa. Morphine sulfate reduced the volume of the contents of the stomach and duodenum promptly and markedly. Glyceryl trinitrate and amyl nitrite did not reduce the duration of time during which bile was not found in the duodenal contents.[62]

Although it is generally believed that pilocarpine injected subcutaneously stimulates the mucus cells of the stomach very considerably but the parietal cells to only a slight extent, Hollander[63] found the opposite to be true.

Assays of the histamine activity extractable from the mucosa of various regions of the human stomach resected for peptic ulcer or carcinoma disclosed a yield from the fundic mucosa averaging 10.2 mg. of histamine and 5.8 mg. from the antral mucosa.[64] In only 3 cases were preparations of both fundic and central mucosa made from the same stomach; the differences were too small to be significant. There were no significant differences between the stomachs that secreted acid, as in peptic ulcer, and those that were achlorhydric, as in carcinoma.

Experiments to confirm the previously reported observation that secretagogues are more potent when applied to the gastric mucosa than when injected intravenously apparently show that they do not act by passing directly into the blood in an unchanged form but do act either in an altered form or by stimulating the elaboration of a gastric hormone.[65]

Hallenbeck[66] investigated the effect of thymoxyethyldiethylamine and N-diethylaminoethyl-N-ethylaniline on the normal gastric secretory process and found that the former did not inhibit the secretory response of Heidenhain pouches to histamine nor significantly alter the response to methyl chloride. Both preparations inhibited the response to the ingestion of a meat meal. In an attempt to find the principle in yeast extract that stimulates gastric secretion, compounds known to be present in yeast, including choline chloride, beta alanine, glutathione and neurine bromide, were tested.[67] Only neurine bromide was definitely active, producing an increase in volume and acidity. The increase in the first thirty minutes was comparable with that of histamine, but the effective dose was one hundred and fifty times greater, being 1.5 mg. per kilogram. The effect of neurine, however, is much more prolonged; hence the response in terms of both volume and acid was more than double that of histamine. Nasio[68] studied the stimulating effect of priscol (a hydrochloride of 2-benzyl-4,5-imidazoline) on gastric secretion and found it to be superior to caffeine and alcohol when given orally and similar to histamine when given parenterally. No local or general reactions

60. Quigley, J. P.; Bavor, H. J.; Read, M. R., and Brofman, B. L.: Evidence that Body Irritations or Emotions Retard Gastric Evacuation, Not by Producing Pylorospasm but by Depressing Motility, J. Clin. Investigation **22**:834-845, 1943.

61. Stevens, N. C.: Functional Vomiting as Interpreted by Auscultation of the Abdomen, New England J. Med. **230**:753-754, 1944.

62. King, H. E.; Comfort, M. W., and Osterberg, A. E.: The Effect of Atropine Sulfate, Pilocarpine Hydrochloride, Prostigmine Methylsulfate, Sodium Salt of Dehydrocholic Acid and Secretin on the Gastric and Duodenal Acid and Duodenal Secretions of Normal Persons When Fasting, Am. J. Digest. Dis. **11**:31-40, 1944.

63. Hollander, F.: The Secretion of Gastric Mucus and Hydrochloric Acid in Response to Pilocarpine, Gastroenterology **2**:201-211, 1944.

64. Trach, B.; Code, C. J., and Wangensteen, O. H.: Histamine in Human Gastric Mucosa, Am. J. Physiol. **141**:78-82, 1944.

65. Butler, D. B.; Hands, A. P., and Ivy, A. C.: Potency of Liver Extract in Stimulating Gastric Secretion by Intravenous Injection and by Direct Lavage, Am. J. Physiol. **139**:325-328, 1943.

66. Hallenbeck, G. A.: Studies on the Effect of Gastric Secretion in Dogs, Am. J. Physiol. **139**:329-334, 1943.

67. Williams, E. F., Jr.; Hoffman, C. F., and Nash, T. P., Jr.: Stimulation of Gastric Secretion by Neurine, Am. J. Physiol. **139**:364-365, 1943.

68. Nasio, J.: (*a*) A New Test for Gastric Function, Rev. Gastroenterol. **11**:174-178, 1944; (*b*) Una nueva prueba funcional gastrica la imidazolina, Arch. argent. de enferm. d. ap. digest. y de la nutrición **19**: 49-56, 1944.

were noted. Roth and Ivy [69] confirmed the observation of earlier investigators that caffeine does not stimulate gastric secretion in the dog. However, when administered by the intravenous route or by lavage of the stomach caffeine does provoke a copious flow of acid gastric juice in the cat, and when administered intramuscularly or by the oral route in man it stimulates gastric secretion.

Davenport,[70] studying the secretion of iodide by the gastric mucosa, concluded that at a plasma concentration below 3 millimols per liter the gastric concentration of iodide is greater than that in the plasma whereas above 3 millimols it is equal to or lower than that in the plasma.

Vorobioff [71] studied the psychogenic inhibition of gastric secretion, with apparently inconclusive results.

By the use of a Coup pouch dog, sodium bicarbonate has been found to increase the volume and the amount of acid in the gastric secretion during the hours immediately following the test meals, with a compensatory decrease during later hours.[72] The feeding of moderate doses of aluminum hydroxide gel three times daily after a test meal results in no depression of secretory activity, either during or after the administration of the antacid.[73] Occasional increases in volume, total chloride, total base and free acid of the pouch secretion occur, but in the majority of experiments these increases are too small to be significant.

After gastroenterostomy and gastric resection only 37.4 per cent of 163 patients had a significant reduction in acidity, although 83.4 per cent had satisfactory clinical results.[74] In 75 patients who had no significant change in the gastric acidity following gastroenterostomy, 75 per cent nevertheless had satisfactory clinical results. Following gastric resection the reduction in acid was proportional to the extent of the resection. However, of patients who had less than half the stomach resected only 25 per cent had a reduction in acidity and 90 per cent had satisfactory clinical results. In the opinion of Heuer and Holman such observations do not controvert the etiologic relationship between acid and ulcer but suggest that it may not be worth while to pursue the goal of achlorhydria by means of larger and larger resections. Perhaps it is better to accept the limitations of resection until a better operation is devised.

Diversion of the entire duodenal content to the stomach does not give effective neutralization, buffering or dilution of the gastric acidity in either the fasting or the digesting state.[75] Hence the slight and infrequent duodenal regurgitation occurring normally can scarcely be an essential factor in controlling intragastric acidity.

Enterogastrone concentrates administered parenterally and endogenous enterogastrone produced by the presence of fat in the intestine produce an inhibition of gastric secretion characterized by a moderate decrease in volume and acid concentration, thus causing a marked decrease in acid output.[76] Pepsin output is moderately depressed by enterogastrone in the absence of vagal influences.

Secretagogues do not act solely by absorption into the blood but cause the release of a hormonal gastric secretory agent. The peptic secretory response of a transplanted pouch to the hormonal stimulus of liver extract introduced into the stomach was not sufficient to cause a pronounced stimulation of pepsin secretion.[77] The results are interpreted as permitting the assumption that histamine could be the hormonal agent responsible for the secretion of pepsin.

Sodium alkyl sulfate decreases the peptic activity of the gastric contents in man when administered in adequate doses in conjunction with a diet low in lipids. The pepsin-inactivating action of sodium alkyl sulfate is inhibited in vitro by cream, butter, lecithin, glycerin and esters

69. Roth, J. A., and Ivy, A. C.: The Effect of Caffeine upon Gastric Secretion in the Dog, Cat and Man, Am. J. Physiol. **141**:454-461, 1944.

70. Davenport, H. W.: The Secretion of Iodide by the Gastric Mucosa, Gastroenterology **1**:1055-1061, 1943.

71. Vorobioff, S.: Los trastornos psicogenos inhibitorios de la secrecion gastrica, Arch. argent. de enferm. d. ap. digest. y de la nutrición **19**:166-182, 1944.

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73. Adams, W. L., and Clark, B. B.: The Effect of Aluminum Hydroxide Gel on Gastric Secretion, Am. J. Physiol. **141**:255-258, 1944.

74. Heuer, G. J., and Holman, C.: The Effect on Gastric Acidity of Gastroenterostomy and Gastric Resection for Peptic Ulcer, Ann. Surg. **118**:551-557, 1943.

75. Kesavalu, A., and Mann, F. C.: The Influence of Duodenal Contents on Intragastric Acidity: An Experimental Study, Surgery **14**:578-587, 1943. Braithwaite, L. R.: The Role of Bile in Duodenal Regurgitation, Brit. J. Surg. **31**:3-13, 1943.

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77. Grossman, M. I.; Woolley, J. R., and Ivy, A. C.: The Pepsin Content of Gastric Juice Secreted in Response to Hormonal Stimulation, Am. J. Physiol. **141**: 506-508, 1944. Barowsky, H.; Upham, R.; Dotti, L. B., and Kleiner, I. S.: The Clinical Significance of the Concentration of Pepsin in Gastric Juice, Rev. Gastroenterol. **10**:201-204, 1943.

of fatty acids with carbon chains of varying lengths.[78]

After implantation in the stomach of a pedicle graft of the jejunal wall, a reversal of the normal secretory response to histamine was found in 4 of 5 dogs and a marked reduction in the fifth. The changes occurred within forty-five minutes and persisted at least four months.[79] In 2 animals after the transplant was resected the reaction to histamine returned to normal within one hour, though in 1 the fasting p_H remained slightly higher than before the transplant was made. In 5 of 6 dogs gastroenterostomy failed to prevent a marked diminution of the average p_H of the mucosa following the injection of histamine, but after conversion of the gastroenterostomy to a jejunal graft the normal response to histamine was reversed in all 6 dogs.[80] Transplants from the ileum and transverse colon were without effect in influencing the p_H of the gastric mucosa after administration of histamine, whereas after transplants from the duodenum and jejunum the p_H of the mucosa after histamine rose significantly.[81] The effect was somewhat more pronounced in the jejunal grafts than it was in the duodenal. When 25 cc. of saline washings of isolated jejunal loops were instilled into the stomachs of normal dogs and withdrawn after ten minutes, there followed a marked depression in the normal response of the gastric acidity to histamine, suggesting an inhibitory substance in the jejunal mucosa.[82] In two later papers [83] these observations were amplified. The rationale of these procedures is very difficult for the reviewers to understand. Teleologically there seems no reason to expect gastric secretion to be modified by an *external* secretion of the intestine. Ivy [84] has repeated and extended the work described by Andrus and his co-workers and has not been able to confirm it. Consequently, final appraisal must be withheld until further studies are made.

Gastroscopy.—Schindler,[85] considering it essential to clarify the gastroscopic criteria of hypertrophic and atrophic gastritis, refutes the statements of Ruffin in 1940 that the characteristic signs of hypertrophic gastritis are influenced by inflation, shows that the role of inflation has been well studied and concludes that its effect on the folds cannot be used as evidence of gastritis. The prolonged vascular engorgement of rugae, causing them to become "intensely red, thick, and turgid," as produced by Wolf and Wolff experimentally, is not the picture of hypertrophic gastritis as it is seen gastroscopically. The gastroscopic criteria for both hypertrophic and atrophic gastritis are restated. In commenting on this paper Ruffin (page 363) raises the question of the gastroscopic appearance of the normal stomach, the effect of emotion and the clinical significance of the changes observed.

Renshaw,[86] considering the roentgenologic and gastroscopic examinations as supplemental and complemental rather than competitive, reviews their relative roles in 938 examinations on 842 patients. The gastroscopic examination was of primary value in the diagnosis for 25.6 per cent. For 17.7 per cent the diagnosis was established by gastroscopy when the roentgenogram was indeterminate, and for 7.9 per cent disease was excluded by gastroscopy when the roentgenogram was indeterminate. Gastroscopy was of secondary value for 55.4 per cent of the patients in that it merely confirmed the diagnosis already made or demonstrated an additional and minor condition. Gastroscopic examination was valueless for 19 per cent of the patients for various reasons, the most common being inability to visualize the area in question. The gastroscopic "blind areas" may be constant or inconstant; hence repetition of the gastroscopic examinations may be of as much value as repetition of the roentgen ray examinations. The accuracy on the

78. Kirsner, J. B., and Wolff, R. A.: Effect of Sodium Alkyl Sulphate on Peptic Activity of Gastric Contents in Man and in Vitro, Proc. Soc. Exper. Biol. & Med. **54**:11-13, 1943.

79. Stefko, P.; Andrus, W. DeW., and Lord, J. W.: The Effects of Jejunal Transplants on Gastric Acidity, Science **96**:208-209, 1942.

80. Andrus, W. DeW.; Lord, J. W., Jr., and Stefko, P.: Comparative Effects of Gastroenterostomy and Pedicle Jejunal Graft on the p_H of the Gastric Mucosa, Proc. Soc. Exper. Biol. & Med. **52**:99-100, 1943.

81. Lord, J. W., Jr.; Andrus, W. DeW., and Stefko, P.: Comparative Effects of Pedicle Grafts from Different Levels of Intestinal Tract on p_H of Gastric Mucosa, Proc. Soc. Exper. Biol. & Med. **52**:100-101, 1943.

82. Andrus, W. DeW.; Lord, J. W., Jr.; Stefko, P., and Dingwall, J. A., III: The Effect of Saline Washings of Isolated Jejunal Loops on Gastric Secretion, Am. J. Physiol. **140**:287-290, 1943.

83. Andrus, W. DeW.; Lord, J. W., Jr., and Stefko, P.: Effects of Pedicle Grafts on Jejunum on the Wall of the Stomach on Gastric Secretion, Ann. Surg. **118**:499-522, 1943. A Possible Mode of Action of Pedicle Jejunal Grafts on Gastric Secretion as Indicated by Changes in p_H of the Surface of the Mucosa of the Stomach, Am. J. Physiol. **141**:75-77, 1944.

84. Ivy, A. C.: Personal communication to the authors; to be published.

85. Schindler, R.: The Gastroscopic Picture of Hypertrophic and Atrophic Gastritis, Gastroenterology **2**:316-322, 1944.

86. Renshaw, R. J. F.: Correlation of Roentgenologic and Gastroscopic Examinations from the Standpoint of the Gastroenterologist, Am. J. Roentgenol. **5**:585-592, 1944.

first examination of the roentgenologic and the gastroscopic diagnosis for 170 patients is compared. For 109 patients, 64.1 per cent, the two methods were in agreement. For 15 the first roentgenologic examination was correct and the gastroscopic indeterminate. For 23 patients the gastroscopist made the first diagnosis. There were 14 patients for whom both methods were indeterminate and 9 patients, 5.3 per cent, for whom both were incorrect. Five per cent of gastric carcinomas are not detected by roentgenologic examination, and benign ulcers not penetrating the mucosa likewise escape detection.[87] Persistent spasm of the antrum taxes the diagnostic acumen of the roentgenologist more than any other condition. A patient considered roentgenologically to have a neoplasm of the antrum with metastasis to the right lung was shown gastroscopically to have a normal stomach. The pulmonary lesion was then diagnosed as a tuberculoma. The patient remained well for over three years. Benedict,[88] in a critical review of gastroscopy, expresses the opinion that examination of the stomach should be done before gastroscopy. Pierson and Pack[89] recommend the vertical position of the patient for gastroscopic examination because it seems to permit better visualization of the fundus and cardia and hence may help to disclose more of the early resectable lesions.

Rafsky[90] combined gastrophotographic studies in natural colors with gastroscopy in the examination of 41 patients. For 26 of the 41 patients the gastrophotographic findings corresponded with the endoscopic findings, but for the other 15 the gastrophotographs did not record the endoscopic findings. For 11 the photographs were blurred because of mucus in the stomach. For 4 the gastric wall was clearly outlined, but the lesion was not visualized because the patient moved or the depth to which the instrument was inserted was miscalculated. The combined examination was considered helpful in the differential diagnosis of benign and of malignant lesions of the stomach, as the contrast on the photographs was distinct. Gastrophotography served as a check on gastroscopy by furnishing a permanent record.

Gastritis. — Schindler[91] studied the correspondence between the gastroscopic findings and the histologic structure of the stomach obtained by biopsies and resections. The surface epithelium of the stomach in the normal state is carefully described, as well as that in chronic superficial gastritis, atrophic gastritis and hypertrophic gastritis. Two kinds of metaplasia were found in atrophic gastritis: (1) the metaplasia of the epithelium of the surface and of the pits into an intestinal type and (2) the metaplasia of the true body glands into a pyloric type of mucus-forming glands. In the hypertrophic form of gastritis, Schindler found the mucosa to be thickened by interstitial infiltration, by extensive proliferation of the surface epithelium or by an enormous increase of the glandular apparatus. Gitlitz and Colp[92] undertook to determine whether any histologic alterations occurred in the wall of the stomach during resection by making a biopsy at the beginning of the operation and comparing it with the resected specimen. No changes of significance were observed in 35 such observations.

Atrophic gastritis may be a deficiency state, particularly of the vitamin B complex.[93] The results of treatment of 5 patients with large doses of thiamine hydrochloride, nicotinamide, riboflavin, pantothenic acid, paraaminobenzoic acid and vitamin A are described. No significant changes in the gastric mucosa as determined by gastroscopic examination were seen, although in 2 of the 5 patients disappearance of the atrophic changes was noted when treatment with choline chloride was given. Further observation will be required to evaluate the effect of choline. Layne and Carey[94] produced black tongue nine times in 5 dogs by means of the Goldberger diet. Severe inflammation of the mucosa of the mouth was not accompanied with similar changes in the gastric mucosa or with significant change in the gastric secretion. Mild hyperemia of the mucosa and decreased tonus were observed early in the experiment. Pallor then developed in all

87. Cohn, A. L., and Levitin, J.: Problems in Gastric Diagnosis: The Gastroscope as an Aid to X-Ray Examination, Gastroenterology **1**:841-854, 1943.

88. Benedict, E. B.: (*a*) A Critical Review of Gastroscopy, Bull. New York Acad. Med. **20**:179-189, 1944; (*b*) Medical Progress—Endoscopy, New England J. Med. **230**:642-647 and 669-676, 1944.

89. Pierson, J. C., and Pack, G. T.: Indications for Vertical Gastroscopy, Rev. Gastroenterol. **11**:111-113, 1944.

90. Rafsky, H. A.: Gastrophotography in Natural Colors in Conjunction with Gastroscopy, Am. J. M. Sc. **206**:618-622, 1943.

91. Schindler, R.: The Surface Epithelium of the Normal and Inflamed Stomach, Gastroenterology **2**: 233-249, 1944.

92. Gitlitz, A. J., and Colp, R.: Gastric Histology and Subtotal Gastrectomy, Ann. Surg. **118**:523-550, 1943.

93. Shapiro, N.; Schiff, L.; Bloch, H. S.; Garber, E. S., and Hannaher, M. J.: Some Observations on Specific Vitamins and Atrophic Gastritis, Gastroenterology **2**:121-132, 1944.

94. Layne, J. A., and Carey, J. B.: The Effect of a Blacktongue-Producing Diet upon the Endoscopic Appearance of the Gastric Mucosa in the Dog, Gastroenterology **2**:133-137, 1944.

except 1 of the animals, but there was no characteristic gross or microscopic alteration.

Gordon [95] reviews the problem of correlation between symptoms and findings in gastritis, indicates the wide variety of opinions experienced and reports on his own series of 78 patients with gastritis, 15 with the hypertrophic type, 8 with the superficial and atrophic, 41 with the superficial and 14 with the atrophic. Five types of symptoms were noted: acute attacks of pain with or without hemorrhage, a syndrome resembling peptic ulcer, early postprandial distress, a syndrome of constitutional inferiority and a syndrome resembling primary anemia. Gordon thinks there are two fairly distinct gastroscopic and clinical entities: hypertrophic gastritis, with symptoms resembling those of peptic ulcer, and atrophic or superficial gastritis, with symptoms of general weakness, numbness and tingling, frequent soreness of the mouth and often achlorhydria.

Browne and McHardy,[96] in evaluating the cases in which a subtotal gastrectomy fails to reveal digestive distress, emphasize the importance of gastroscopic examination as the only satisfactory method of studying the gastric mucosa and of making a diagnosis of postoperative gastritis. The therapeutic regimen suggested consists of a high protein, relatively bland diet approximating 4,000 calories a day supplemented by the parenteral administration of vitamins B and C and liver extract, together with the use of aluminum hydroxide and an antispasmodic.

Annis [97] performed gastroscopic examination on 276 of 2,142 patients with gastrointestinal disease seen at Camp Blanding, Florida, and found some form of gastritis in 109 (39.5 per cent); hypertrophic changes, in 52; superficial changes, in 44, and atrophic changes, in 13. The observed gastroscopic change did not correspond with any definite clinical history. The diagnosis of psychoneurosis was made by the psychiatrist much more commonly for persons with chronic dyspepsia with a normal gastric mucosa than for persons with gastritis. Therapy was not of definite value, as judged either by the clinical course or by the results of gastroscopic examination. Annis is convinced "that the patient with chronic gastritis is likely to be a military disability. Indeed it is hard to think of a form of chronic dyspepsia, organic or functional, which does not prevent the individual from becoming an effective field soldier." Guyer [98] compared the roentgenologic and gastroscopic findings on 200 consecutive dyspeptic soldiers in the British Army. The roentgenologic analysis was as follows: normal, 73.5 per cent; duodenal ulcer, 8.5 per cent; duodenitis, 7.5 per cent; gastric ulcer, 3.5 per cent; gastritis, 2.5 per cent; other findings, 4.5 per cent. The gastroscopic analysis yielded the following results: normal, 47 per cent; gastritis (all types), 44 per cent; gastric ulcer, 3.5 per cent; healed gastric ulcer, 4.5 per cent; adenoma, 0.5 per cent. In an analysis of 61 cases of gastritis it was found that in 29.5 per cent the disease was of the mild superficial type; in 45.9 per cent, of the severe active superficial type; in 19.6 per cent, of the atrophic type, and in 4.6 per cent, of the hypertrophic type. It was very noticeable that nearly all the patients said they had suffered from dyspepsia in civil life but had been able to carry on with their occupations as long as they were in a position to have the type of diet which suited their individual requirements. Alkalis had been prescribed medically or had been purchased spontaneously by practically every one. Symptoms were uniform, consisting of a complaint of indefinite epigastric pain, generally after meals, relieved by vomiting. The striking feature in all cases was the poor mental outlook and the state of general depression, with complaints of weakness, headaches and inability to compete with others during their military training.

Feldman [99] reports a most unusual case of hypertrophic gastritis with giant gastric rugae producing a filling defect suggestive of carcinoma roentgenologically.

A fatality occurred after use of tetracaine hydrochloride (2 per cent) as an anesthetic gargle in preparation for gastroscopic procedures on a patient with carcinoma of the esophagus and extensive metastases to the liver.[100]

Hypertrophic Pyloric Stenosis.—Two cases of hypertrophic pyloric stenosis are reported because of the rarity of the condition in adults and because of the possibility that psychogenic fac-

95. Gordon, W.: The Symptoms Associated with Chronic Gastritis, Gastroenterology **1**:1013-1021, 1943.

96. Browne, D. C., and McHardy, G.: Postgastrectomy Gastritis, Ann. Int. Med. **20**:789-792, 1944.

97. Annis, J. W.: Gastritis in the Military Service, Gastroenterology **2**:85-92, 1944.

98. Guyer, R. B.: The Comparison of Radiological and Gastroscopic Findings in 200 Dyspeptic Soldiers, Brit. J. Radiol. **16**:241-246, 1943.

99. Feldman, M.: Giant Gastric Rugae with Diffuse Hypertrophic Gastritis: A Case Resembling a Neoplasm on the Lesser Curvature of the Stomach, Radiology **41**:181-183, 1943.

100. Hansen, F. M., Jr., and Stealy, C. L.: Sudden Death Following the Use of Pontocaine as a Gargle Anesthetic for Gastroscopic Examination, Rev. Gastroenterol. **10**:212-213, 1943.

tors may play an etiologic role.[101] Both patients were aggressive, ambitious and driving, and both were beset by social and financial problems. When confronted with distressing situations which would arouse anxiety in a normal person, both of them were conscious of somatic distress. The patients gave a comparatively brief ulcer-like history with symptoms of partial pyloric obstruction. Gastric resection was done on both because carcinoma could not be excluded. Pathologic examination disclosed hypertrophic muscle and infiltration of the stomach with plasma cells suggesting gastritis although the gastroscopic examination revealed nothing abnormal. Wakefield[102] describes the case of a 52 year old white man with painless nausea and vomiting for thirty years until cured by resection of a hypertrophied pylorus. Vance[103] gives a brief but comprehensive review of 27 cases of congenital pyloric stenosis.

Foreign Bodies.—Benedict[104] reports on a 3 year old girl who swallowed an open safety pin and then, while awaiting operation, vomited the pin. Jenkins[105] describes a soldier who had vague biliary symptoms of only thirty-six hours' duration. At operation a gangrenous, perforated gallbladder impacted with over 200 stones, complete fibrous obliteration of the cystic and common bile ducts, fibrous obliteration of the distal portion of the hepatic duct and general peritonitis were found. After complete postoperative recovery, the hepaticogastric fistula was demonstrated roentgenographically two months later.

Syphilis.—A case of well proved extensive secondary syphilis is noteworthy primarily because of the gastroscopic studies.[106] "The mucosa was hyperemic and edematous throughout. There were numerous submucosal hemorrhages of all sizes and shapes. A few superficial erosions were seen and there was much adherent mucus. The impression was that of a chronic superficial gastritis." A month later "no mucosal hemorrhages were seen. The anterior and posterior wall together with the lesser and greater curvatures presented a dull mucosa. This dullness was patchy. On the anterior wall of the body of the stomach the mucosa presented a patchy, gray, thin appearance, and some large submucosal blood vessels were visible. The chronic superficial gastritis was present at this time." Unfortunately, a later examination was not possible. The evidence that the changes noted were due to syphilis is presumptive.

Actinomycosis.—Shearburn[107] reports proved actinomycosis of the stomach with duodenal ulcer asymptomatic for eighteen months. It is the only case found in the literature in which the patient lived more than one year after operation. A case of subphrenic actinomycotic abscess with persistent infection is also reported and presumed to be the result of actinomycotic infection resulting from perforation of a peptic ulcer. In neither case was it possible to prove whether the mycosis was the primary cause of the ulcer or whether there was a secondary invader.

Fibrosis.—Under the heading of gastric fibrosis involving the duodenum, Silverman and Friedman[108] describe the case of a 40 year old white man who complained of intermittent pain in the epigastric area for fourteen years, with periods of remission; the epigastric pain was sharp, occasionally radiating to the infracapsular area bilaterally and to the midline on the same level; sometimes it was so severe that it awakened him at night. Ingestion of food relieved the pain for about an hour. The roentgenologic examination showed what appeared to be a polyp in the duodenal cap and a more irregular filling defect in the first portion of the duodenum, the walls of which were extrinsically smooth and well rounded. Gastric resection was performed. On microscopic examination extensive fibrosis of the submucosa was found, extending between the muscle bundles and including the subserosal surface of the stomach. No malignant cells were identified. The case is presented as an instance of localized fibrosis of the stomach and duodenum. The history, however, is that of peptic ulcer; the photographs suggest the presence of a deformity of the ulcer type at the junction of the first and second portions of the duodenum; at operation "a stellate scar was found on the anterior surface of the duodenum" thought to be the site of an old ulcer, and hence one wonders if the fibrosis may not have been secondary to a duodenal ulcer or, perhaps, to additional healed gastric ulcers.

101. Berk, E., and Dunlap, H. J.: Hypertrophic Pyloric Stenosis in Adults, Ann. Surg. **119**:124-133, 1944.

102. Wakefield, H.: Hypertrophic Pyloric Stenosis in Adults, Gastroenterology **2**:250-257, 1944.

103. Vance, C. A.: Congenital Pyloric Stenosis, Ann. Surg. **119**:351-359, 1944.

104. Benedict, E. B.: Vomiting of an Open Safety Pin, New England J. Med. **230**:484, 1944.

105. Jenkins, H. B.: Spontaneous Hepatogastric Biliary Fistula, J. A. M. A. **123**:830-832 (Nov. 27) 1943.

106. Spellberg, M. A., and Norfleet, W. J.: Early Gastric Syphilis, Gastroenterology **2**:191-194, 1944.

107. Shearburn, E. A.: Actinomycosis of the Stomach and Duodenum: Report of Two Cases, Surgery **14**:38-46, 1943.

108. Silverman, D. N., and Friedman, L. L.: Gastric Fibrosis Involving the Duodenum, Gastroenterology **2**:186-190, 1944.

Surgery for Functional Disturbances.—Subtotal gastrectomy was done in 1 case and resection of the ascending colon in another by Strelinger [109] for gastrointestinal disease of uncertain nature, with the argument that in exceptional circumstances such a procedure is justifiable. The cases presented are not convincing.

PEPTIC ULCER

Historical.—Goldstein [110] gives an interesting and well illustrated account of ulcer and cancer in the Middle Ages.

Incidence.—Tidy [111] studied the crude death rates during the period 1912 to 1938 for peptic ulcer in various districts in the British Isles and found little or no rise in the years between 1912 and 1920, a rapid rise between 1921 and 1930 and no further rise between 1930 and 1938.

Etiology.—Davidoff [112] reports 12 more cases of coexistent lesions of the central nervous system and the gastrointestinal tract.

In a discussion of the pathologic physiology of gastric and duodenal ulcer, Shay [113] presents the results of a thorough study made by him and his associates of the gastric, motor and secretory functions in normal human subjects and in patients with peptic ulcer, emphasizing the role of local gastric and duodenal mechanisms. The introduction into the duodenum of hydrochloric acid, hypertonic saline solution, hypertonic dextrose solution, olive oil and cream inhibited gastric secretion. These results are more pronounced in normal persons and in persons with healed duodenal ulcer than in patients with active ulcer, thus leading Shay to suggest that the return of gastric motor and secretory functions to normal is probably the only reliable criterion of healing in a duodenal ulcer. The therapeutic value of milk and cream in the ulcer diet probably rests in part on the inhibitory effect of fat. Glaessner,[114] on the basis of the stimulation of gastric inhibitory secretion by insulin and the inhibition of gastric secretion resulting from the injection of dextrose into the duodenum or jejunum, argues for a very important connection between gastric secretion and blood sugar in which hepatic function plays an important role. He interprets the rarity of peptic ulcer (0.25 per cent) in diabetic persons and the frequency of achlorhydria (33.3 per cent) as further evidence. The mechanism of the stimulation of the gastric secretion by insulin is not clear, but the inhibition from the intraduodenal administration of dextrose is apparently that elaborated by Shay.

McHardy and Browne [115] report 2 cases of duodenal ulcer developing apparently after so-called "histamine desensitization" and thought to afford clinical confirmation of the experimental production of peptic ulcer with histamine. This is in contrast to Horton's report of healing during the process of "desensitization." McHardy and Browne consider Horton's evidence insufficient and more than offset by the 2 cases described by them.

The same authors describe a pair of identical twins in whom duodenal ulcer developed at identical periods in their lives.[116] This observation is thought to add weight to the theory of "constitutional predisposition." Bearing on this same topic is the report [117] of a familial history of digestive disease in 340 (21.8 per cent) of 1,617 patients with duodenal ulcer and 636 patients with gastric ulcer, from which it is concluded that there is no familial predisposition in the localization of peptic ulcer. Boros,[118] on the other hand, argues for a constitutional predisposing factor because of a family of eleven children in which the mother, four of the nine sons and one of the two daughters all had ulcer with massive hemorrhage, as did the daughter of the eldest son. In the opinion of the reviewers, papers of this type would be improved by a study such as Barnett's statistical analysis of the familial incidence of anacidity.[119]

The diets of 16 patients with chronic ulcer were found to be poorly balanced and deficient in food energy value as well as in thiamine and ascorbic acid.[120]

109. Strelinger, A.: Major Resection for Functional Gastrointestinal Disease: Report and Evaluation of Two Cases, Am. J. Surg. **62**:72-79, 1943.

110. Goldstein, O. I.: Ulcer and Cancer of the Stomach in the Middle Ages, J. Internat. Coll. Surg. **6**:482-490, 1943.

111: Tidy, H.: Course of Death Rate from Peptic Ulcer in Great Britain, 1912-1938, Brit. M. J. **1**:677-682, 1944.

112. Davidoff, L. M.: The Influence of the Nervous System on the Gastro-Intestinal Tract, Rev. Gastroenterol. **11**:102-105, 1944.

113. Shay, H.: The Pathologic Physiology of Gastric and Duodenal Ulcer, Bull. New York Acad. Med. **20**: 264-291, 1944.

114. Glaessner, C. L.: Gastric Secretion and Sugar Metabolism, Am. J. Digest. Dis. **10**:307-313, 1943.

115. McHardy, G., and Browne, D. C.: Duodenal Ulcer Developing in Man Following "Histamine Desensitization," Gastroenterology **2**:345-347, 1944.

116. McHardy, G., and Browne, D. C.: Duodenal Ulcer Concomitant in Identical Twins, J. A. M. A. **124**:503 (Feb. 19) 1944.

117. Bonorino Undaondo, C., and Nasio, J.: La herencia en la úlcera gástrica y duodenal, Prensa méd. argent. **31**:223-233, 1944.

118. Boros, E.: Familial Peptic Ulcer Hemorrhage, Am. J. Digest. Dis. **11**:45-47, 1944.

119. Bloomfield, A. L., and Polland, W. S.: Gastric Anacidity, New York, The Macmillan Company, 1933, p. 59.

Collins [121] made a detailed study of gastric glands in 13 surgically resected stomachs. Degeneration, necrosis and repair were observed in stages of gradually increasing severity and magnitude, suggesting a single disease process. The most minimal changes were scattered glands lined with epithelial cells not differentiated into chief and parietal cells, together with scattered glands containing cells undergoing a process of vacuolar degeneration. These changes were thought to be compatible with the normal process of degeneration and repair. Degeneration was sometimes associated with infiltration of polymorphonuclear leukocytes, perhaps involving a number of adjacent glands and resulting in focal necrosis. The most advanced stage was ulceration and scarring involving all the layers of the stomach. When the degeneration was overwhelming and the repair inadequate, peptic ulcer resulted. When the degeneration was long continued with exhaustion of the germinal epithelial cells, atrophic gastritis resulted. The paper is reminiscent of earlier workers in this country and abroad, notably those of Konjetzny and Puhl.

Nedzel [122] considers the "spasm theory" of peptic ulcer to be the most logical one to explain the periodicity of the lesion. Experiments consisting of the administration of a single injection or repeated injections of pitressin intravenously were made on 62 dogs. Negative results were obtained in 39 (63 per cent) and positive results in 23 (37 per cent). The latter group showed lesions of the stomach and duodenum ranging from a small erosion to a large ulcer. Direct observation through an incision of the abdomen and stomach to observe the effect of the pitressin disclosed contraction of the stomach and the formation of petechial hemorrhages. "For about thirty to forty-five minutes, especially after two or three injections of pitressin, the small hemorrhages definitely began to resemble small erosions and the mucosa became hyperemic with the folds disappearing."

In a further study, Lord, Andrus and Stefko [123] used the histamine and beeswax technic for the production of peptic ulcer. In 2 normal control dogs given 120 mg. of histamine daily for thirty days multiple erosions of the duodenum developed, whereas 2 dogs with jejunal transplants similarly treated were found at necropsy to have normal gastrointestinal tracts. Six normal dogs and 1 with a jejunal transplant were then given histamine daily and observed for seven weeks. In all the 6 normal dogs hyperemia of the duodenum developed; in 3, ulcerations extending into the muscularis, and in 3, multiple erosions. The dog with the jejunal transplant was found at autopsy after the seven weeks to have a normal stomach and duodenum. One of the animals given histamine began to have tarry stools on the eighth day and was operated on on the twelfth day. A duodenotomy disclosed several punctate erosions. A jejunal transplant to the stomach was carried out. On the twenty-sixth postoperative day autopsy revealed a normal gastric and duodenal mucosa, even though the daily administrations of histamine had been continued. The lesions produced in the control animals do not appear to the reviewers to have been of a magnitude comparable with those produced by others using this technic. Hence the influence of the jejunal transplant is difficult to assess. Furthermore, as mentioned earlier, Ivy has not been able to confirm the alleged inhibitory effect of jejunal transplants on gastric secretion.

Ivy,[124] in discussing recent experimental developments pertaining to the clinical management of peptic ulcer, reports on pyrogen-free preparations of enterogastrone which prevented the development of peptic ulcer in Mann-Williamson dogs. Furthermore, the animals failed to have ulcer for at least one year after treatment was discontinued. The enterogastrone preparation does not depress the gastric secretion of acid or pepsin in response to an alcohol test meal, although it does greatly reduce the excessive continued fasting secretion. Ivy advances the hypothesis that enterogastrone increases the resistance of the jejunal mucosa to ulceration. In 15 patients with two or more recurrences of peptic ulcer annually, palliative results were obtained by the administration of the enterogastrone preparation. Sandweiss [125] similarly reports that the principle in urine described by him as possessing prophylactic and therapeutic properties against Mann-Williamson ulcers immunizes against the formation of ulcer. In 6 Mann-

120. Riggs, H. E.; Reinholt, J. G.; Boles, R. S., and Shore, P. S.: The Diet and Chronic Peptic Ulcer, J. A. M. A. **124**:639-641 (March 4) 1944.

121. Collins, V. P.: The Peptic Ulcer and Chronic Gastritis, Ann. Surg. **118**:1005-1014, 1943.

122. Nedzel, A. J.: Experimental Production of Gastric Ulcers in Dogs by Inducing Vascular Spasm with Pitressin, Am. J. Digest. Dis. **10**:283-296, 1943.

123. Lord, J. W., Jr.; Andrus, W. DeW., and Stefko, P. L.: Effects of Jejunal Transplants on Experimental Production of Peptic Ulcers, Arch. Surg. **46**: 459-464 (April) 1943.

124. Ivy, A. C.: Some Recent Developments in the Physiology of the Stomach and Intestine Which Pertain to the Management of Peptic Ulcer, Bull. New York Acad. Med. **20**:5-14, 1944.

125. Sandweiss, D. J.: The Immunizing Effect of the Anti-Ulcer Factor in Normal Human Urine (Anthelone) Against the Experimental Gastrojejunal (Peptic) Ulcer in Dogs, Gastroenterology **1**:965-969, 1943.

Williamson dogs given intramuscular injections of from 1 to 5 mg. of the antiulcer substance (not urogastrone) in normal human urine daily for a period of one year or longer ulcers failed to develop eleven months after therapy was withdrawn (1 mg. represented 60 cc. of urine). This is interpreted as a long-standing immunity not due to depression of gastric secretion. The name "anthelone" (Greek *ἀντί* against; *ἕλκος* ulcer) is proposed for the substance described in order to differentiate it from the urogastrone factor, which does inhibit gastric secretion and motility. This approach to the problem of the therapy of peptic ulcer is intriguing in its possibilities, and hence the results of further study are eagerly awaited.

Trauma.—Fowler [126] estimates the incidence of primary ulcer resulting from a single blunt trauma at 0.6 per cent and presents 9 litigated cases in which peptic ulcer allegedly was due to trauma. The verdicts were equally divided, with 1 compromise. In the opinion of Fowler there are a few cases in which fresh lesions revealed at operation or autopsy may undeniably be of primary traumatic origin, but more frequently such an origin cannot be proved. Furthermore, a preexisting ulcer may be reactivated by direct abdominal trauma or indirectly by neurosis resulting from the injury. Kinmonth [127] reports the interesting case of a 15 year old boy crushed between two wagons who at operation was found to have a laceration 3 cm. long in the anterior wall of the stomach involving the seromuscular layers only, and half a pint (0.25 liter) of blood in the left infracolic compartment due to a complete tear in the mesentery of the small intestine. The patient three weeks later had melena and hematemesis. At the second operation an ulcer somewhat larger than a sixpence was found in the center of the site of the injury with several small bleeding vessels in the floor of the ulcer.

Roentgenology.—Feldman,[128] in discussing the problem of the roentgenoligic diagnosis of duodenal ulcer in inductees, stresses the early mucosal changes. Borman,[129] commenting on the infrequency of peptic ulcer in the descending duodenum and the rarity with which it is diagnosed roentgenologically, attributes the error of the roentgenologist to inadequate study of the duodenum and to failure in differentiating the lesion from diverticulums or barium sulfate retained in the lateral recess of a deformed duodenal bulb. Seven cases are reported of active ulcer in the upper descending duodenum, located on the upper and inner margin of the descending duodenum usually just below the superior flexure, with secondary spasm, mucosal distortion and medial retraction of the adjacent upper descending duodenum. Hemorrhage was a prominent feature in 6 of the cases and nocturnal pain in 4. Kahlstrom [130] reports a duodenal ulcer measuring 5 by 4 cm. at autopsy. Two interesting cases of benign ulcer with decided shortening of the lesser curvature of the stomach are described.[131] Preiss [132] reports a benign ulcer of the greater curvature, with excellent roentgenograms and histologic confirmation; Señorans [133] describes a similar lesion observed gastroscopically and roentgenologically over a period of nine months, with complete healing.

Illustrating the variety of disease seen in one person, Moreno [134] reports the case of a 55 year old man with pulmonary and laryngeal tuberculosis who had had a tuberculoma of the cecum removed; eleven years later carcinoma of the flexure followed. Three years later a benign gastric ulcer with gastritis developed.

Treatment.—Portis [135] discusses the clinical significance of emotional disturbances as well as organic factors in the development of gastritis, duodenal irritation and duodenal ulcer and urges evaluation of both the somatic and the psychologic factors in their treatment. Bolen,[136] in a study of 40 patients, emphasizes the importance of relieving emotional stress and hence concludes that mental anxiety and strain play an important role in the causation of peptic ulcer. Winkel-

126. Fowler, R. H.: External Trauma and Peptic Ulcer, Indust. Med. **12**:614-632, 1943.

127. Kinmonth, J. B.: Abdominal Injuries Leading to Gastric Ulceration and Haematemesis in a Boy of 15, Brit. J. Surg. **31**:93-94, 1943.

128. Feldman, M.: Responsibility of the Roentgenologist in the Wartime Duodenal Ulcer Problem, Radiology **42**:356-358, 1944.

129. Borman, C. N.: Ulcer in Descending Duodenum, Am. J. Roentgenol. **50**:752-764, 1943.

130. Kahlstrom, S. C.: Giant Ulcer of the Duodenum, M. Bull. Vet. Admin. **20**:451-452, 1944.

131. Señorans, A. J.; Gñi Moreno, I., and Aguirre, J. A.: Desplazamiento y fijación plástica de visceras por úlceras escleroretractiles del estómago, Arch. argent. de enferm. d. ap. digest. y de la nutrición **19**:13-35, 1944.

132. Preiss, A.: A Case of Peptic Ulcer on the Greater Curvature of the Stomach, Brit. J. Radiol. **17**:182-184, 1944.

133. Señorans, A. J.: Ulcera gástrica de la curvadura mayor, Arch. argent. de enferm. d. ap. digest. y de la nutrición **18**:533-545, 1943.

134. Moreno, J.: Sobre interpretación radiológica de una úlcera gástrica tratamiento médico, Arch. agent. de enferm. d. ap. digest. y de la nutrición **19**:150-165, 1944.

135. Portis, S. A.: The Clinical Significance of Emotional Disturbances Affecting the Stomach, Duodenum and Biliary Tract, Psychosom. Med. **6**:71-73, 1944.

136. Bolen, H. L.: The Emotional Factor in Peptic Ulcer, Rev. Gastroenterol. **10**:187-191, 1943.

stein,[137] in reviewing the various treatments of peptic ulcer, rates the continuous intragastric drip of milk and soda as the best type of medical therapy and partial gastrectomy combined with vagotomy as the most valuable form of surgical treatment. Driscoll and Aaron [138] present a series of 100 cases of peptic ulcer treated by fourteen different acceptable methods. Relief was obtained in 81 of the 100 cases. Hence the conclusion was reached that except for cases of complicated or intractable ulcer any treatment will give results provided it is followed intelligently. "Successful treatment depends upon cooperation of the physician and the patient, and the control of gastric acidity by diet and antacids." The in situ action of the antacids was studied in 17 patients with duodenal ulcer by means of intubation of the first portion of the duodenum, and it was found that while the oral administration of an antacid in the usual therapeutic dose does reduce the acidity of the contents of the first part of the duodenum the reduction is neither great nor long lasting and may be followed by a rebound increase.[139]

Demole and Guye [140] used the synthetic adrenal substance desoxycorticosterone in the treatment of about 40 patients with ulcer. Pain disappeared after the second or third injection, even in patients who had been resistant to ordinary treatment. The characteristic roentgenologic appearance was completely altered in fifteen or more days. Only 1 of the patients failed to respond. The late results of desoxycorticosterone therapy were not so favorable as the immediate effects, particularly in case of chronic ulcer. There was only 1 with permanent result among 11 patients with old ulcers. Of 10 patients who had the ulcer for less than a year, 8 were permanently cured. In general, a relapse followed after from four to ten months in more than half of the patients.

Metz and Lackey [141] report "satisfactory clinical results" in 74 per cent of 418 unselected patients with uncomplicated peptic ulcer treated with intranasal insufflation or desiccated posterior pituitary powder as a supplement to "rational medical management."

Fogelson and Shoch [142] have studied the treatment of gastroduodenal ulcerative disease with sodium alkyl sulfate, with the thought that inactivation of pepsin rather than alteration of gastric acidity might permit healing of the ulcer. Of the numerous substances belonging to the large group of detergents investigated for their ability to inhibit peptic activity in dilute concentration without altering acidity, sodium alkyl sulfate was found to be one of the most effective and most available. When this substance was fed at intervals of ten hours in doses of 0.1 Gm. to dogs given daily injections of histamine and beeswax, the survival time of the dogs was prolonged to well over two hundred days in approximately half of the animals. This survival period was attributed to inactivation of the pepsin. As a control the authors accepted the observation of others that the survival period of such dogs is not over thirty days. Sodium alkyl sulfate was shown to be nontoxic to dogs when given in doses of 2 Gm. a day for ten months and when given to human beings in a dose of 1 Gm. daily for eight weeks. The clinical study consisted in the administration of sodium alkyl sulfate in doses of 0.2 Gm. apparently at hourly intervals although not specifically stated. In a series of 34 patients with ulcer considered "intractable," there were 26 who had satisfactory results and 8 for whom failure resulted. "In most of the patients responding to sodium alkyl sulfate there was marked improvement within ten days although no result was classified as a failure until the treatment had been given a thirty day trial."

Steigmann and Marks [143] were unable to confirm the alleged lowering of peptic activity in the presence of an unaltered p_H. The antacids calcium carbonate, aluminum hydroxide and magnesium hydroxide caused a more pronounced inhibition than did the detergent. The clinical use of sodium lauryl sulfate failed to reveal any superiority over the other medications used. The pepsin-inactivating action of sodium alkyl sulfate is inhibited in vitro by cream, butter, lecithin, glycerin and esters of fatty acids with carbon chains of varying length.[144] Kirsner and Wolff [145]

137. Winkelstein, A.: The Modern Treatment of Peptic Ulcer, Bull. New York Acad. Med. **20**:87-98, 1944.

138. Driscoll, E. F., and Aaron, A. H.: Response to Treatment of Peptic Ulcer, New York State J. Med. **44**:266-269, 1944.

139. Berk, J. E.; Rehfuss, M. E., and Thomas, J. E.: In Situ Effects of Antacids in Duodenal Ulcer, Arch. Int. Med. **72**:46-57 (July) 1943.

140. Demole, M., and Guye, P.: La cortine dans le traitement de l'ulcère gastro-duodénal, Praxis **32**:517-519, 1943.

141. Metz, M. H., and Lackey, R. W.: Peptic Ulcer Treated with the Aid of Posterior Pituitary Extract, South. M. J. **36**:747-750, 1943.

142. Fogelson, S. J., and Shoch, D. E.: Treatment of Gastroduodenal Ulcerative Disease with Sodium Alkyl Sulfate, Arch. Int. Med. **73**:212-216 (March) 1944.

143. Steigmann, F., and Marks, A. R.: Inhibition of Peptic Activity in the Treatment of Peptic Ulcer, Am. J. Digest. Dis. **11**:173-178, 1944.

144. Kirsner, J. B., and Wolff, R. A.: Effect of Sodium Alkyl Sulfate on Peptic Activity of Gastric Contents in Man and in Vitro, Proc. Soc. Exper. Biol. & Med. **54**:11-13, 1943.

145. Kirsner, J. B., and Wolff, R. A.: Effect in Vitro of Various Detergents on Peptic Activity of Human Gastric Content, Gastroenterology **2**:270-273, 1944.

in further in vitro studies found a number of anionic detergents which do not inhibit peptic activity, two which have a moderate effect and two, Duponol PC and Naccanol E, both anionic detergents, which inhibit peptic activity as decidedly and as effectively as commercial sodium alkyl sulfate. In a carefully conducted clinical study [146] in which sodium alkyl sulfate was administered together with milk and cream, hourly doses of 130, 260, 390 and 520 mg. did not produce a lowering of peptic activity. However, when the sodium alkyl sulfate was given in doses of 780 mg. (!) at hourly intervals with a low fat diet there was an appreciable, although temporary, decrease. No toxic effects except mild diarrhea were noted. Kirsner and Wolff [147] apparently used three to five times as much sodium alkyl sulfate as reported by Fogelson and Shoch. No beneficial effect was observed on 1 large gastric ulcer after twenty-eight days of treatment, on a second after thirty-eight days and on a third after twenty-five days. The patients had all been under observation for some months and offered, therefore, an unusual opportunity for controlled study. Kirsner and Wolff concluded that sodium alkyl sulfate given hourly in large doses in conjunction with milk and cream does not produce a detectable decrease in the peptic activity of the gastric contents in human beings; that given hourly in large doses in conjunction with a diet low in fat it may decrease appreciably though temporarily the peptic activity, and that the healing of gastric ulcer is not affected by the use of very large quantities of sodium alkyl sulfate and a low fat diet.

Gill and Keele,[148] in studying the efficiency of milk and the various alkalis usually used in the treatment of peptic ulcer, concluded that adequate neutralization of peptic activity is obtained by raising the p_H of the gastric juice to 3.5 to 4.0 and that milk, magnesium carbonate, calcium carbonate, tribasic magnesium and calcium phosphates, colloidal aluminum hydroxide and magnesium trisilicate are the most satisfactory agents.

Upham and Chaikin,[149] in a clinical investigation of the aluminum phosphate gel, found that in patients with an already disturbed calcium and phosphorus metabolism the administration of excessive amounts may produce an actual loss of phosphate. The optimum dose in the treatment of peptic ulcer is considered to be 2 tablespoons every two hours and 6 tablespoons before retiring.

Alkalosis. — Zintel, Rhoads and Ravdin [150] found that ammonium chloride can be administered intravenously to patients with alkalosis without evident harm and that it is effective in rapidly lowering the serum carbon dioxide at the rate of approximately 1 volume per cent for each gram administered. Two per cent solutions were prepared by dissolving 20 Gm. of ammonium chloride in a liter of water, 0.9 per cent sodium chloride solution or 5 per cent dextrose solution. The ammonium chloride and sodium chloride solutions could be autoclaved, but the dextrose solutions acquired a brownish color suggestive of caramelization and were not used.

Surgical Treatment.—For duodenal ulcer gastric resections exceeded gastroenterostomies in number at the Mayo Clinic during 1942.[151] About 17 per cent of the patients with duodenal ulcer and 60 per cent of those with gastric ulcer were treated surgically. DeCourcy [152] reviews his experience with the ulcer problem. Stewart and Zaepfel [153] discuss the use of subtotal gastric resection in cases of bleeding and penetrating gastric ulcer and those in which malignancy cannot be definitely excluded.

Connell [154] reports a case of recurrent intractable duodenal ulcer treated by a partial fundusectomy on Dec. 14, 1931, with no recurrence of ulcer distress up to the time of the report, July 1943. In 24 other cases with the same type of operation there were 2 postoperative deaths and 2 in which the remote result is unknown. In 19 of the remaining 20 cases the patients have been symptom free. In 1 remaining case recurrent symptoms developed in six months; a second operation disclosed an old duodenal ulcer, for which pyloroplasty was performed. The author considers the clinical results

146. Kirsner, J. B., and Spitzer, E. H.: Further Studies on the Effect of Sodium Alkyl Sulfate on Peptic Activity, Gastroenterology **2**:348-353, 1944.

147. Kirsner, J. B., and Wolff, R. A.: The Effect of Sodium Alkyl Sulfate on the Peptic Activity of the Gastric Contents and on the Healing of Gastric Ulcer in Man, Gastroenterology **2**:93-101, 1944.

148. Gill, A. M., and Keele, C. A.: Pepsin Inactivation in Ulcer Therapy, Brit. M. J. **2**:194-196, 1943.

149. Upham, R., and Chaikin, N. W.: A Clinical Investigation of Aluminum-Phosphate Gel, Rev. Gastroenterol. **10**:287-297, 1943.

150. Zintel, H. A.; Rhoads, J. E., and Ravdin, I. S.: The Use of Intravenous Ammonium Chloride in the Treatment of Alkalosis, Surgery **14**:728-731, 1943.

151. Walters, W.; Gray, H. K.; Priestley, J. T., and Counseller, V. S.: Annual Report on Surgery of the Stomach and Duodenum for 1942, Proc. Staff Meet., Mayo Clin. **18**:505-510, 1943.

152. DeCourcy, J. L.: Present Status of Gastric and Duodenal Ulcer, Am. J. Surg. **61**:11-15, 1944.

153. Stewart, J. D., and Zaepfel, F. M.: Surgical Aspects of Gastric Ulcer, New York State J. Med. **44**: 611-616, 1944.

154. Connell, F. G.: Partial Fundusectomy (Proximal Gastrectomy): Review of Twenty-Four Cases, Ann. Surg. **118**:1000, 1943.

in the 19 cases as satisfactory, despite the return of normal gastric acidity, motility and size in the 5 other cases studied.

Massive Hemorrhage.—Rasberry and Miller [155] support the prompt feeding program for grossly bleeding peptic ulcer with adequate fluid intake to avoid shock and blood transfusions when necessary. To the 32 cases previously reported on the authors add 43, making a total of 75 personally observed and included in 2,111 cases described in the literature in which treatment consisted in some form of frequent feeding program. The gross mortality is 4 per cent and the net mortality 1.9 per cent. Surgical intervention for bleeding ulcer should be considered only when there is evidence of coincident perforation. Manzer [156] describes 2 cases of bleeding gastric ulcer, in 1 in a man aged 67 and in the other in a man aged 72, successfully controlled surgically and 1 fatal case in which the ulcer was not found at operation. Schiff [157] reports on the treatment in 160 cases of bleeding peptic ulcer with a modified Meulengracht diet. Approximately half the patients received blood transfusions. The overall mortality was 6.8 per cent and the mortality from exsanguination 3.1 per cent.

Rafsky and Weingarten [158] analyzed a series of 476 cases of bleeding peptic ulcer to evaluate the role of hypertension and found that the severity of the hemorrhage was little affected. The gross mortality in patients under 50 years with hypertension was increased, but this was attributed to complicating diseases not found in the patients without hypertension. In patients over 50 years of age the mortality with and without hypertension was approximately the same.

Maldonado-Allende [159] reports a case of rather severe hematemesis and melena of unproved origin occurring in a patient with brucellosis.

Jejunal Ulcer.—Tepper and Massell,[160] in discussing the treatment of gastrojejunocolic fistula, emphasize the opinion that the final procedure should include gastric resection, because anything short of this is likely to result in a therapeutic failure.

Acute Perforation.—A statistically significant increase in perforated peptic ulcer was found during the period of heavy air raids in London as compared with the previous three and the following two years.[161] The average number of perforations per month from January 1937 to August 1940 ranged from 22 to 25.5, but in months from September 1940 to May 1941 the average jumped to 35.11. In the subsequent nine months the average was 20.3, with a further decrease to 16.5 for the following periods. The statistical evidence is thus in favor of the view that some general tendency operated to cause perforations during the air raid period. Anxiety may have constituted an important cause. A significant and unexplained increase in perforations was also found in the month of December in the prewar years.

Raw [162] studied a series of 312 cases of perforated gastric and duodenal ulcer with a gross mortality of 14.4 per cent. The two most important factors influencing operative mortality were the age of the patient and the interval before the operation. Supraclavicular pain was presented in 60 per cent of the cases of perforated ulcers and was of great diagnostic help.

Wakeley,[163] in a follow-up of 103 patients with perforated peptic ulcer operated on between 1924 and 1934 found that 44 per cent are still serving in the Royal Navy; only 8 per cent of these men had died, as compared with 20 per cent of a comparable series of civilians; therefore the person with perforated peptic ulcer need not be invalidated from the service.

McCabe and Mersheimer,[164] in studying 89 cases of acute gastroduodenal perforations found that the diagnosis was correctly made preoperatively in 89.7 per cent. In cases in which the diagnosis could not be made by the symptoms and results of physical and roentgenologic examinations the determination of the serum amylase to exclude pancreatitis and the ingestion of methylthionine chloride by stomach tube followed by peritoneal aspiration of the dye with a

155. Rasberry, E. A., Jr., and Miller, T. G.: The Prompt Feeding Program for Bleeding Gastric and Duodenal Ulcer: A Report of 2,111 Collected Cases Including 75 Personally Observed, Gastroenterology **1**:911-921, 1943.

156. Manzer, T. T.: Surgical Treatment of Massive Gastroduodenal Hemorrhage, Northwest Med. **43**:112-113, 1944.

157. Schiff, L.: The Treatment of Bleeding Peptic Ulcer with a Report of 160 Cases Treated by a Prompt Feeding Program, South. M. J. **37**:535-542, 1944.

158. Rafsky, H. A., and Weingarten, M.: The Effect of Hypertension on the Prognosis of Bleeding Peptic Ulcer, Rev. Gastroenterol. **11**:93-101, 1944.

159. Maldonado-Allende, I.: Hemorragías digestivas en el curso de la brucelosis, Arch. argent. de enferm. d. ap. digest. y de la nutrición **18**:470-477, 1943.

160. Tepper, G. B., and Massell, T. B.: Management of Gastrojejunocolic Fistula, Am. J. Surg. **61**:434-438, 1944.

161. Spicer, C. C.; Stewart, D. N., and Winser, D. M.: Perforated Peptic Ulcer During the Period of Heavy Air-Raids, Lancet **1**:14, 1944.

162. Raw, S. C.: Perforation of Gastric and Duodenal Ulcers, Lancet **1**:12-14, 1944.

163. Wakeley, C. P. G.: Late Results of Perforated Peptic Ulcer, Lancet **1**:11-12, 1944.

164. McCabe, E. J., and Mersheimer, W. L.: Acute Gastroduodenal Perforations: Review of Metropolitan Hospital Series 1930-1941, Am. J. Surg. **62**:39-49, 1943.

spinal puncture needle served as valuable diagnostic adjuncts.

Williams,[165] in a follow-up of 100 cases of acutely perforated peptic ulcer repaired surgically, found that after an average period of three years and four months the result was considered excellent in 28 per cent, good in 27 per cent, fair in 22 per cent and poor in 23 per cent of the cases. Ashton[166] reports the case of a man 80 years of age in whom operation was performed for a perforated duodenal ulcer three and one-half hours after onset, with recovery. Paletta and Hill[167] review a series of 83 cases of patients with acute perforation of gastric or duodenal ulcer operated on between 1925 and 1942. The mortality was 16.9 per cent. The mortality in the group with gastric ulcer was twice that in the group with duodenal ulcer. Patients over 50 years of age showed a mortality six times that of patients under 50 years of age. The mortality of patients operated on after twelve hours was 25 per cent, compared with 13.6 per cent for the group operated on twelve hours or sooner after perforation. Jackson and Metheny[168] give a brief review of 30 cases of perforated peptic ulcer. Estes and Bennett[169] report 80 consecutive cases of acute perforated gastroduodenal ulcer with an operative mortality of 8.7 per cent. Reperforation occurred in 8 (12.7 per cent). Of the 53 in which end results were studied there was complete cure in only 5.6 per cent; in 71.7 per cent medical treatment was required for control of the recurrent ulcer, and in 22.8 per cent further surgical measures or hospitalization was required.

Burden,[170] on the basis of his personal experience, advocates gastroenterostomy in addition to closure of the acute perforation. Bertola and Martinez[171] report on 6 perforated ulcers treated surgically by wide gastric resection, with good results. Warren and Fallis[172] report 3 cases of acute perforation of postoperative jejunal ulcer. The first of these is particularly noteworthy in that the patient first experienced a perforation of a duodenal ulcer. Eighteen months later a partial gastrectomy was performed, approximately four-fifths of the stomach being removed. About twenty months later a jejunal ulcer perforated and was repaired surgically, but it perforated again seven months later. In the second case an acute perforation of a duodenal ulcer was repaired, and a year later a posterior gastroenterostomy for pyloric stenosis was performed. A jejunal ulcer perforated almost three years later. The perforation in the third case occurred after anterior gastroenterostomy with enteroenterostomy.

Pearce,[173] in discussing the value of pain in the shoulder, obliteration of hepatic dulness and the fluoroscopic demonstration of pneumoperitoneum, advocates in the diagnosis of perforated peptic ulcer, the Trendelenburg and reversed Trendelenburg positions as valuable in demonstrating these signs.

Ulcer in Childhood.—Copello[174] cites a number of historical references on peptic ulcer in childhood and reports an ulcer of three years' duration in a boy 14 years of age, treated by fundusectomy and without recurrence for the follow-up period of two years. Benner[175] reports 7 cases of duodenal and 1 of gastric ulcer found on postmortem examination in children from 2 days to 11 years of age. One case was remarkable because of the association of ulcer with possible rhubarb poisoning. Two apparently healed ulcers were found. Hutchins[176] reports a case of acute perforation of a duodenal ulcer in a 9 year old white girl, with recovery following operation.

Ulcer and Military Service.—Edwards and Copeman,[177] in analyzing the cases of 356 patients complaining of dyspepsia in a military hos-

165. Williams, A. C.: Perforated Peptic Ulcer: A Follow-Up Study of One Hundred Cases, New England J. Med. **230**:785-790, 1944.

166. Ashton, G. W.: A Case of Perforated Duodenal Ulcer with Recovery in a Man Aged Eighty Years, M. J. Australia **1**:130, 1944.

167. Paletta, F. X., and Hill, W. R.: Acute Perforated Gastric and Duodenal Ulcers, Surgery **14**:32-37, 1943.

168. Jackson, L. E., and Metheny, D.: Thirty Cases of Perforated Peptic Ulcer, Northwest Med. **42**:367-368, 1943.

169. Estes, W. L., Jr., and Bennett, B. A. Jr.: Acute Perforation in Gastroduodenal Ulceration, with Special Reference to End-Results, Ann. Surg. **119**:321-341, 1944.

170. Burden, V. C.: Acute Perforated Ulcer, Am. J. Surg. **63**:61-68, 1944.

171. Bertola, V. J., and Martinez Carreras, A.: Ulceras perforadas gastroduodenales. Gastrectomía, Prensa méd. argent. **30**:2287-2297, 1944.

172. Warren, K. W., and Fallis, L. S.: Perforation of Postoperative Jejunal Ulcers, Surgery **15**:569-573, 1944.

173. Pearce, A. E.: Diagnosis of Perforated Ulcer. Two Useful Maneuvers by Means of Which Pneumoperitoneum and Diaphragmatic Irritation Are Demonstrated More Clearly, Am. J. Surg. **61**:76-78, 1944.

174. Copello, O.: Peptic Ulcer in Childhood, Prensa méd. argent. **30**:2275-2280, 1943.

175. Benner, M. C.: Peptic Ulcers in Infancy and Childhood: Post-Mortem Studies of Eight Cases; One Case of Possible Poisoning by Rhubarb, J. Pediat. **23**: 463-470, 1943.

176. Hutchins, L. R.: Peptic Ulcer in Children: Case Report of Perforation, Northwest Med. **43**:40-41, 1944.

177. Edwards, H., and Copeman, W. S. C.: Dyspepsia: An Investigation, Brit. M. J. **2**:640-642, 1943.

pital, found 139 with peptic ulcer, 37 with other organic disease and 180 with diagnoses of a functional disorder. The duration of freedom from pain after food was longer in the group with ulcer than in the group without. The pain was relieved by food in nearly three quarters of the patients with ulcer but in less than half of those without ulcer. Nocturnal pain was a more pronounced feature of ulcer dyspepsia than of nonulcer dyspepsia. Annis and Eldridge,[178] in reviewing the cases of patients admitted to an outpatient gastrointestinal clinic at a station hospital during a two year period, found that the incidence of peptic ulcer was not greatly different than that seen in civilian practice and that the ratio of duodenal to gastric ulcer was approximately 15 to 1. Aitken[179] reports that 4.5 per cent of all the men reporting sick in an armored regiment during a two year period were patients with dyspepsia, 45 per cent of whom were referred to hospitals for further investigation. Of these, 36 per cent were found to have gastroduodenal ulceration and 17 per cent gastroduodenitis. Tidy[180] considers the prevalence of dyspepsia, organic and nonorganic, in the army in the present war to be comparable to the incidence in the civilian population. Peptic ulcer began in civilian life in 81 per cent of the soldiers studied. The recurrence in the army is ascribed to unavoidable routine. Peptic ulcer caused 58 per cent of the admissions to the hospital for dyspepsia. Men with it are not suitable for army life, whereas men suffering from nonorganic dyspepsia can in many cases make useful soldiers provided they are not hospitalized too long.

Kirk,[181] in an interesting study of 50 cases of duodenal ulcer and 1 of gastric ulcer encountered at Fort Sill, makes the following comment regarding the psychosomatic aspect of the ulcer problem:

"Actually only three men developed acute and primary onset of symptoms within the 12 months preceding induction and hospitalization. In no case could a definite relationship be established with the prospect of certain military service. Wolff's[182, 183] ulcer case histories showed prolonged emotional turmoil involving mainly conflict, anxiety, guilt, hostility and resentment! Every medical officer has seen a certain number of soldiers who have had all the above emotions with the possible exception of guilt, admittedly preceding the following induction in the army. On the gastrointestinal service these soldiers fitting this description very closely have in almost every instance been hospitalized for pernicious vomiting, but in no single case has a duodenal ulcer been demonstrable.

"Of the 11 soldiers developing ulcer symptoms for the first time while in service, it is easy to say that failure to obtain a promotion, transfer to less desirable posts, 'alerting' for foreign service, constant and unremitting obedience to orders can satisfactorily establish the background of their ulcer. Actually in only a few of the psycho-neurotic personalities did these factors predominate. Outstanding was a history of onset of gastrointestinal complaints while on maneuvers eating field rations. Even overnight field problems on field rations could be relied on to produce exacerbations. Further doubt seems cast on the emotional concept of the genesis of ulcer by the inescapable fact, at least in this hospital, that patients with proven duodenal ulcer respond promptly on standard ulcer management. Complete relief of severe pain within 48 to 72 hours after being put on strict management was the rule rather than the exception. Quite the reverse occurred in the 'typical psychoneurotics.' No relief was admitted by the great majority when they were hospitalized for many weeks and either sent to duty or released from the military service on surgeon's Certificate of Disability for Discharge."

Chamberlin[184] attempts to standardize the diagnosis and treatment of peptic ulcer. Walters and Butt[185] urge further study of the value of radical surgical treatment of peptic ulcer in officers and specialists in whom ulcer develops while they are on active duty, so that more may be returned to active duty. Reports from 1,352 patients with peptic ulcer admitted to naval hospitals indicated that 92 per cent were treated medically, 55 per cent of whom were returned

178. Annis, J. W., and Eldridge, F. G.: Military Gastroenterology, South. M. J. **36**:791-798, 1943.

179. Aitken, D. G.: Dyspepsia and the Sick Parade: One Hundred and Forty-One Cases in an Armored Regiment, J. Roy. Army M. Corps **81**:223-230, 1943.

180. Tidy, H.: Peptic Ulcer and Dyspepsia in the Army, Brit. M. J. **2**:473-477, 1943.

181. Kirk, R. C.: Peptic Ulcer at Fort Sill, Am. J. Digest. Dis. **10**:411-413, 1943.

182. Wolf, S., and Wolff, H. G.: Evidence on the Genesis of Peptic Ulcer in Man, J. A. M. A. **120**: 670-675 (Oct. 31) 1942.

183. Mittelmann, B., and Wolff, H. G.: Emotions and Gastroduodenal Function, Psychosom. Med. **4**:5-61, 1942.

184. Chamberlin, D. T.: A Plan for Standardization of Diagnosis and Treatment of Peptic Ulcer, Mil. Surgeon **93**:157-164, 1943.

185. Walters, W., and Butt, H. R.: (*a*) Management of Ulcers Among Naval Personnel, Ann. Surg. **118**: 489-498, 1943; (*b*) The Treatment of Naval Personnel with Peptic Ulcer, U. S. Nav. M. Bull. **41**:1679-1682, 1943.

to active duty, whereas 71 per cent of those treated surgically were returned to active duty. In a personal series of 35 patients 22 were treated medically, 73 per cent being returned to duty, while of 13 treated surgically 85 per cent returned to duty. Partial gastric resection was done in 85 per cent. It was noted that 25 per cent of those discharged from the navy with medical treatment had been hospitalized repeatedly. Hence radical surgical treatment is advocated for chronic recurring ulcers developing during service because the incidence of recurrence is less than the 25 per cent now found for such ulcers treated medically.

Rush [186] found that 53 per cent of 200 patients admitted to a large hospital in the South Pacific because of "dyspepsia" had functional disorders. The most characteristic complaint of these patients was distress induced by the taking of food. For the most part the therapeutic response was poor, leading Rush to the conclusion that such patients should be returned to the zone of the interior.

GASTRIC CANCER

Incidence.—Mulsow,[187] studying the incidence of cancer in Iowa, found that in the city of Cedar Rapids cancer of the stomach caused 12.3 per cent of all deaths from cancer; in the cancer clinic at the Iowa State Hospital, 5.3 per cent, and in the report of the Division of Vital Statistics for the State of Iowa in 1941, 15.2 per cent of all such deaths. It is difficult to reconcile these figures with others, such as those of Cramer [188] and Mullen,[189] which ascribe 30 and 35 per cent respectively of the total cancer mortality to cancer of the stomach.

Dorn [190] found that in 48 per cent of the white males and 74 per cent of the white females in whom cancer develops, the growth originates in either the digestive or the genital system. Among females the genital system is attacked most frequently, while in males the most frequent localization is in the digestive system. The incidence of cancer of the digestive tract in white males is 60 per cent higher than that in white females.

Experimental Production.—Kirby [191] and his associates in work on the experimental production of gastric cancer found that cancer did not develop in rats fed cholesterol heated to 300 C., thus refuting the theory of Roffo that cholesterol either irradiated or heated undergoes an oxidative process whereby polycyclic hydrocarbons arise which are carcinogenic for mice. In stock mice given an adequate diet with the addition of either 3,4-benzpyrene or 20-methylcholanthrene papilloma of the forestomach with a tendency to malignant evolution developed. Unlike the diffuse gastropapillomatosis associated with dietary deficiency, the papillomas induced with carcinogenic hydrocarbons tend to be localized and invasive and are not prevented or influenced by the addition of vitamin A to the diet.[192] In rats receiving an adequate basal diet with the addition of either the residue of cholesterol heated to 300 C. or 3,5-cholestadiene gastric tumors failed to develop.[193]

Gastritis and Cancer.—Alvarez [194] describes the case of a 55 year old man with mild abdominal discomfort and low gastric acidity for fifteen years who died of gastric cancer nineteen months after an ulcerative gastritis was found gastroscopically.

While Konjetzny [195] thinks that approximately 85 per cent of all gastric cancers develop on the basis of gastritic mucosal changes, Westhues,[196] as a result of a study of 463 resected stomachs and 40 stomachs obtained at necropsy, concludes that inflammation is not the decisive factor in the development of gastric cancer. He does not deny the possibility of cancer arising from gastritis, but he questions its frequency. Blastomatous gastric polyps are definitely precancerous,

186. Rush, A.: Gastrointestinal Disturbances in the Combat Area: II. Preliminary Observations on Functional Disorders of the Digestive Tract, J. A. M. A. **123**:471-473 (Oct. 23) 1943.

187. Mulsow, F. W.: Low Incidence of Cancer of the Stomach in Iowa, Am. J. Digest. Dis. **10**:297-300, 1943.

188. Cramer, W.: Origin of Cancer in Man, J. A. M. A. **119**:309-316 (May 23) 1942.

189. Mullen, T. F.: Factors Influencing the Curability of Cancer of the Stomach, Surg., Gynec. & Obst. **72**:297-306, 1941.

190. Dorn, H. F.: Illness from Cancer in the United States: IV. Illness from Cancer of Specific Sites Classed in Broad Groups; V. Illness from Cancer of Individual Specific Sites, Pub. Health Rep. **59**:33 and 65, 1944.

191. Kirby, A. H. M.: Attempts to Induce Stomach Tumors: I. The Effects of Cholesterol Heated to 300° C., Cancer Research **3**:519-525, 1943.

192. Peacock, P. R., and Kirby, A. H. M.: Attempts to Induce Stomach Tumors: II. The Action of Carcinogenic Hydrocarbons on Stock Mice, Cancer Research **4**:88-93, 1944.

193. Kirby, A. H. M.: Attempts to Induce Stomach Tumors: III. The Effects of (*a*) a Residue of Cholesterol Heated to 300° C., and (*b*) 3,5-Cholestadiene, Cancer Research **4**:94-97, 1944.

194. Alvarez, W. C.: Cancer of the Stomach Arising in Gastritis, Proc. Staff Meet., Mayo Clin. **18**: 225-226, 1943.

195. Konjetzny, G. E.: Der Magenkrebs, Stuttgart, Ferdinand Enke, 1938.

196. Westhues, H.: Entstehung des Magencarcinoms aus Gastritis und entzündlichen Polypen? Arch. f. klin. Chir. **203**:391-435, 1942.

but they are not inflammatory; hence cancers developing in them are not a result of inflammation.

Guiss and Stewart,[197] after a careful review of the literature and a detailed histologic study of stomachs obtained from persons of all ages from birth to senility with and without gastric or extragastric cancer arrive at important conclusions:

"Intestinal metaplasia, pyloric gland heterotopia, mucosal cyst instances of dedifferentiation of specialized cells and lymphoid collections are not present at birth and must therefore develop postnatally, probably as a result of mucosal damage. Intestinal metaplasia, heterotopia of the pyloric glands, mucosal cysts, heavy leukocytic infiltration and large numbers of lymphoid aggregates are never found in truly normal stomachs but are all evidences of gastritis changes. Stomachs of patients who died of cancer other than gastric cancer are essentially identical with those who died from other causes, except that they contain fewer lymphoid follicles and collections, and less leukocytic infiltrate. This difference is directly proportional to the degree of malnutrition present and not due to the presence of cancer itself in the patient. Eighty-two per cent of stomachs from apparently normal persons who died within the gastric cancer age (over 40) show microscopic evidence of chronic atrophic gastritis. Ninety-seven per cent of stomachs with gastric carcinoma show associated chronic atrophic gastritis. There is a similar incidence of chronic atrophic gastritis in association with gastric diseases other than carcinoma. The chronic atrophic gastritis associated with gastric carcinoma is a non-specific 'reaction' to inflammation and gastric injury in general, and there is no evidence to suggest an etiologic relationship other than that chronic atrophic gastritis may be caused or intensified by the presence of carcinoma in the stomach.

"The factors included in the present concept of chronic atrophic gastritis, i. e. mucosal atrophy, increased amounts of leukocytic infiltrate and lymphoid aggregates, intestinal metaplasia and pyloric gland heterotopia are all rather closely correlated, variation in one factor tending to be associated with proportionate changes in the others. This correlation probably justifies the consideration of these changes as a pathologic entity.

"The often reiterated claim that chronic atrophic gastritis is a precancerous lesion receives no positive support as a result of this study. The slight difference in incidence of gastric atrophy between cancerous and noncancerous stomachs is far from being convincing. Atrophic gastritis is an exceedingly common condition with advancing age. Mere statistical correlation of incidence of gastric atrophy and of gastric cancer is quite insufficient to show causal relation. Both atrophy and cancer appear to be events in aging organs. Were the effort made, it would doubtless be easy to show that gastric cancer was correlated not only with gastric atrophy but likewise with atrophy of other organs even in fact with atrophy of such anatomically unrelated structures as the genitalia, breasts, circulatory apparatus or even skin, thus reducing to absurdity the conclusions based on mere statistics as to incidence.

"To assert on morphologic grounds that the origin of gastric cancer depends on the existence of gastric atrophy would require far more evidence. It would at least require proof that early gastric cancer begins in, and can be directly traced to, an area of atrophy to the exclusion of other areas. From the very nature of gastric material universally available in large clinics, this type of evidence, although it may eventually appear, will be long in coming. Could even this be proved correct, the larger question would still remain unanswered as to why A, with gastric atrophy, gets cancer and B, with the same atrophy, does not. Prematurity in formulating important conclusions in matters of this sort is unjustified."

On the other hand, Warren and Meissner[198] point out that the histologic changes in chronic gastritis should be divided into exudative and epithelial; the former have no direct significance as a precancerous lesion, but the latter when severe may be comparable to well recognized premalignant lesions elsewhere in the body. Hence these authors assume that some gastric cancers arise on this basis, even though conclusive statistical proof is not available.

Prognosis and Classification.—Dochat and Gray[199] studied the cases of 1,251 patients with gastric carcinoma operated on at the Mayo Clinic between the years 1922 and 1934. The tumors were classified into four types based on the extent of the lesion: type A, those in which the carcinoma involves only the mucosa and is not seen

197. Guiss, L. W., and Stewart, F. W.: Chronic Atrophic Gastritis and Cancer of the Stomach, Arch. Surg. **46**:823-843 (June) 1943.

198. Warren, S., and Meissner, W. A.: Chronic Gastritis and Carcinoma of the Stomach, Gastroenterology **3**:251-256, 1944.

199. Dochat, G. R., and Gray, H. K.: Carcinoma of the Stomach: Prognosis Based on a Combination of Duke's and Broders' Method of Grading, Am. J. Clin. Path. **13**:441-449, 1943.

microscopically below the muscularis mucosae; type B_1 lesions are those in which the carcinoma extends from the submucosa into the muscularis and involves all or part of the gastric musculature; type B_2 lesions have spread through the entire wall and involved the serosa; type C lesions include those in which there is metastatic involvement of the regional lymph nodes. The survival rate graded in this manner was compared with the survival rate graded by the method of Broders. It was found that the grade of the lesion and the extent of its spread taken together give a better index of the duration of postoperative life than does one of these methods alone.

Puderbach and Ficarra [200] report a gastric tumor described histologically as a "malignant carcinoid" although the silver stains were unsatisfactory. From a practical viewpoint the differentiation is not too important, except that carcinoids and indeed certain adenocarcinomas are generally very slow in growth and metastasis.

Wood,[201] in an interesting discussion of adenocarcinoma of the pyloric end of the stomach, presents 2 cases with metastases in the lymph node containing squamous cells as well as glandular components and reviews 19 cases reported in the literature. In discussing the mechanism of their development, Wood reviews the experimental studies of Stewart and Lorenz and other workers and concludes that "direct neoplastic stimulation of undifferentiated basal cells in the gastric mucosa is . . . the essential factor in the histogenesis of squamous cell tumors of the pyloric region of the stomach."

Natural History.—Palmer,[202] commenting on the meagerness of knowledge of the natural history of gastric carcinoma, emphasizes the greatest variations in the rate of growth and extension. The extremes are represented by the "acute" growths, such as the rapidly metastasizing tumors described by Jarcho, and the very "chronic lesions" such as that described by Eusterman and Balfour in which the patient was operated on nine and one-half years after the onset of symptoms, two and one-half years after a diagnosis of gastric carcinoma was made, and yet a resectable lesion was found. The patient was still alive and well nine years later. Palmer describes another case with fairly good evidence of gastric cancer for eleven years. In a third instances a lesion identified roentgenologically and gastroscopically as a small ulcerating carcinoma was observed for four years with 16 roentgenologic examinations and 22 gastroscopic examinations before resection was carried out. Symptoms were minimal and there was no loss of weight. The resected lesion was a small ulcerated mucinous carcinoma without evidence of metastasis. The factors determining or influencing these various rates of growth are unknown, although in general the biologic behavior of the tumor corresponds roughly with the degree of cellular differentiation in terms of Broder's grading. The therapeutic implication is that as a rule gastric carcinoma should be resected unless there exist proved distant metastases. There is very little evidence to support the view that the removal of the primary tumor exerts a favorable influence on the growth of secondary lesions.

Feldman [203] reports 3 instructive cases of long-standing carcinoma of the stomach. In the first, that of a 56 year old man with slight dyspeptic symptoms of two years' duration, a roentgenogram of the stomach disclosed a seemingly insignificant prepyloric narrowing. In 5 further roentgen ray examinations during seventeen years, progressive narrowing was noted. At operation an inoperable carcinoma was found. In the second case, a 59 year old man gave a history of digestive complaint extended over a period of three years. The roentgen ray examination at the time of the first symptoms revealed a slight and seemingly insignificant narrowing of the prepylorus. Two years later with a recurrence of symptoms, roentgenologic examination again revealed a "spastic pylorus and narrowing of the prepylorus thought to be due to a gastritis." One year later "roentgen studies revealed a partial pyloric obstruction with an annular infiltrating ulcerating carcinoma. At operation an inoperable carcinoma was found." In the third case, a man 73 years old when admitted to the hospital was followed during six years. Four sets of roentgenograms in this period showed the progressive narrowing of the pylorus, caused, as proved at operation, by an inoperable carcinoma. The 3 cases are well documented with roentgenograms and constitute further convincing evidence of the chronicity of certain gastric carcinomas.

200. Puderbach, W. J., and Ficarra, B. J.: Malignant Carcinoid of the Stomach: Case Report of a Patient Treated by Subtotal Gastrectomy, Am. J. Surg. **61**:121-123, 1943.

201. Wood, D. A.: Adenoacanthoma of the Pyloric End of the Stomach, Arch. Path. **36**:177-189 (Aug.) 1943.

202. Palmer, W. L.: The Duration of Gastric Cancer, Gastroenterology **1**:723-736, 1943.

203. Feldman, M.: The Life Cycle of Carcinoma of the Stomach, Gastroenterology **2**:60-64, 1944.

Alvarez [204] reports the case of a man with an old duodenal ulcer who was found at operation to have a leather bottle type of stomach with a malignant ulcer which was excised near the cardia. Two years later another such ulcer was found.

Fergusson [205] reports on a 39 year old patient with carcinoma of the stomach invading the right ureter and producing a urinary extravasation on the right side as the result of the obstruction of the ureter.

Diagnosis.—Wasch and Epstein [206] call attention to the double contrast method of detecting carcinoma of the cardia roentgenologically. The tumor mass may be clearly demonstrated in the air bubble with the stomach empty or only partially filled with barium sulfate solution. Better contrast roentgenograms were obtained by inflating the stomach with air through a Levine tube.

Jenkinson and Latteier [207] report 2 instructive cases in which spasm of the antrum produced the roentgenologic criteria of gastric carcinoma. An interesting case is described of gastric carcinoma not diagnosed by gastroscopic or roentgenologic examination but nevertheless found at operation to be present and invading both the pancreas and the spleen.[208]

A most interesting experiment [209] in the early diagnosis of gastric carcinoma consists in the mass roentgenologic study of 2,413 men and women over the age of 50 who had no digestive symptoms of appreciated significance. Of these, 491 were reexamined a year or more later. Three were found to have unsuspected malignant gastric tumors, 2 of them having a carcinoma and 1 a lymphosarcoma. All 3 underwent subtotal gastric resection. The lymphosarcoma was not found by the surgeon at operation but was found on reoperation several months later. One of the two carcinomas situated near the pylorus presented an ulcerated area less than 1 cm. in diameter. It had entered the muscularis at only one area and had not metastasized. The method of study was a rapid fluoroscopic examination of the stomach in an effort to differentiate between the abnormal and the normal. In the cases in which the stomach did not appear normal, a subsequent, more detailed, examination was made. The chief difficulty encountered was not the speed of the examination itself but the handling of the patients, guiding them back and forth from the dressing rooms, keeping them moving steadily into the fluoroscopic room, etc. Two assistants and a stenographer were required to keep the examiner busy. The cost of examination was approximately 48 cents per person; this did not include a charge for the service of the roentgenologist or overhead charges for the equipment, but merely the actual cost of secretarial and technical help, stationery, films, etc. An interesting by-product was the relatively large number of abnormalities other than carcinoma disclosed, such as 54 instances of deformity of the duodenal bulb with or without crater, 7 of cardiospasm and 25 of diaphragmatic hernia. Whether or not these results warrant for the mass of the populace routine roentgenologic examination of the stomach at intervals is questionable, but they certainly emphasize the importance of roentgenologic examination, the need for an examination at the slightest indication and the low cost with which such examinations can be made on a quantity basis.

Thorstad [210] reviews 970 cases of malignant gastric neoplasms observed from 1928 to 1942 in a private and in a charity hospital. Of the patients observed in the private hospital 42.3 per cent were clinically inoperable, as compared with 76.6 per cent in the charity hospital. Gastrectomy was performed on 19.4 per cent of the patients at the private hospital and in 9.8 per cent of those at the charity hospital. No evidence was found to indicate a significant improvement in either the diagnosis or the treatment of early carcinoma of the stomach during this fifteen year period.

Bolen [211] describes a pattern in the dried red blood cell which not only is a "sensitive indicator" of the presence of carcinoma but "can be used at intervals to determine the course of the disease, presence of metastases, and end results after surgery, deep x-ray therapy, or radium implantation." The evidence offered is not convincing to the reviewers.

204. Alvarez, W. C.: Benign Appearing Ulcers Coming Repeatedly in a Leather Bottle Stomach: Report of Case, Proc. Staff Meet., Mayo Clin. **18**:298-299, 1943.

205. Fergusson, J. D.: Ureteral Stricture with Perinephric Urinary Extravasation Caused by Metastases from a Silent Carcinoma of the Stomach, Brit. J. Surg. **31**:283-286, 1944.

206. Wasch, M. G., and Epstein, B. S.: The Roentgen Visualization of Tumor of the Cardia, Am. J. Roentgenol. **51**:564-571, 1944.

207. Jenkinson, E. L., and Latteier, K. K.: Non-Organic Gastric Filling Defects Simulating Carcinoma, Radiology **41**:444-450, 1943.

208. Case Records of the Massachusetts General Hospital, Cabot Case 30092, New England J. Med. **230**: 264-266, 1944.

209. St. John, F. B.; Swenson, P. C., and Harvey, H. D.: An Experiment in the Early Diagnosis of Gastric Carcinoma, Ann. Surg. **119**:225-231, 1944.

210. Thorstad, M. J.: The Outlook on Carcinoma of the Stomach, Am. J. Surg. **64**:242-247, 1944.

211. Bolen, H. L.: Diagnostic Value of Blood Studies in Malignancy of the Gastrointestinal Tract, Am. J. Surg. **63**:316-323, 1944.

Surgical Treatment.—In 127 malignant tumors observed by Amesti [212] between 1938 and 1942 the resectability rate was 55.76 per cent with a mortality of 26 per cent. Metheny [213] concludes that at least 50 per cent should be subjected to operation, and the surgeon must be willing to accept a high mortality rate. When 50 per cent of 42 tumors were operated on, 12 resections were done, with a mortality of 50 per cent and a chance of cure of 14.5 per cent. When 30 per cent of 67 malignant tumors were operated on, 10 per cent were resected, with a 25 per cent mortality and a 7.5 per cent chance of cure. When only 10 per cent of 34 tumors were operated on, 8 per cent were resected, with no mortality and a 10 per cent chance of cure.

Morris [214] reviews the history of surgical treatment of gastric carcinoma from the time of Billroth to the present day, notes that at Bellevue Hospital there have been three times as many admissions for gastric carcinoma as for gastric ulcer and estimates that the incidence of resectable carcinoma in the United States is about 10,000 per year, and yet only 3,000 resections have been reported in this country. The American College of Surgeons has 1,279 registered five year cures. Twenty per cent of the patients dying from carcinoma of the stomach show no distant metastases at autopsy. In the last twenty years at the Charity Hospital in New Orleans, the resectability rate has more than doubled while the operative mortality has been cut to one third of that ten years ago. Morris estimates that 50 per cent of the patients seen in the hospitals have cancers which are inoperable. that only 25 per cent have resectable cancer and that 20 per cent of those with resected tumors may be expected to survive for more than five years.

These estimates reflect the present status, but there is much reason to hope that in the years to come the number of resectable carcinomas will greatly exceed the present figure of 25 per cent, that the five year cures will likewise increase and that the mortality rate will decrease. Thus Walters and his associates [215] report that resection was carried out on 40 per cent of the patients operated on for malignant disease in the year 1942, with a mortality rate of 6.7 per cent, the lowest in the records of the Mayo Clinic.

Allen [216] reports that 14 per cent of 255 gastric ulcers thought to be benign proved to be malignant microscopically. Healing of the ulcer under adequate medical management did not assure the absence of malignancy. When operation was done with a clinical diagnosis of cancer, the five year cure rate was 20 per cent; whereas when operation was undertaken with a diagnosis of ulcer and cancer found, the cure rate increased to 40 per cent. The five year cure rate including mortality as reviewed in 1933 and 1939 has not been appreciably improved, but an increased number of patients have had more months of respite from symptoms.

Lahey and Marshall [217] describe 73 patients who underwent total gastrectomy at the Lahey Clinic, with a mortality of 33 per cent; in the last two years in 28 operations the mortality was reduced to 18 per cent. Most postoperative deaths were due to intra-abdominal infection. Microscopic examination of the lymph nodes disclosed metastatic involvement in 87 per cent of the cases with resection. Of the 48 patients surviving gastrectomy, 15 lived more than a year and 7 have lived two or more years. One patient is alive and well after four and one-half years, and another is well after six years. These figures for survival are to be contrasted with the average life expectancy of five months for patients with such tumors when no resection is carried out. Clagett and Root [218] report an adenocarcinoma of the cardia in a young woman 21 years of age successfully treated by transthoracic resection. Eight such operations were performed, with 1 postoperative death. Sweet [219] reports 7 similar cases.

Because of the bacteriologic flora found in the stomachs of patients with gastric carcinoma, the use of 5 to 10 Gm. of sulfathiazole preoperatively is advised.[220]

212. de Amesti, F.: Malignant Tumors of the Stomach, Am. J. Surg. **63**:78-85, 1944.

213. Metheny, D.: Curability of Gastric Carcinoma, Northwest Med. **42**:17-18, 1943.

214. Morris, H. J.: End Results in Surgical Treatment of Gastric Carcinoma, New Orleans M. & S. J. **96**:254-262, 1943.

215. Walters, W.; Gray, H. K.; Priestley, J. T., and Counseller, V. S.: Annual Report on Surgery of the Stomach and Duodenum for 1942, Proc. Staff Meet., Mayo Clin. **18**:505-511, 1943.

216. Allen, A. W.: Benign and Malignant Ulcers of the Stomach, Bull. New York Acad. Med. **20**:15-24, 1944.

217. Lahey, F. H., and Marshall, S. F.: Indications for an Experience with Total Gastrectomy Based upon Seventy-Three Cases of Total Gastrectomy, Ann. Surg. **119**:300-320, 1944.

218. Clagett, O. T., and Root, G. T.: Transthoracic Resection of the Cardia of the Stomach, Proc. Staff Meet., Mayo Clin. **19**:187-191, 1944.

219. Sweet, R. H.: Total Gastrectomy by the Transthoracic Approach: Report of Seven Cases, Ann. Surg. **118**:816-837, 1943.

220. Priestley, J. T.; Thompson, L., and Sealy, W. B.: Bacteriologic Aspects of Gastric Contents in Presence of Surgical Lesions of the Stomach and Duodenum, Proc. Staff Meet., Mayo Clin. **19**:1-4, 1944.

A defective diet and chronic loss of blood are not considered sufficient to explain the hypoproteinemia and anemia.[221] Patients who have had total gastrectomy for cancer have an impaired ability either to digest or to absorb fat in the diet.[222] The blood lost during various gastrointestinal operations is not excessive when compared with that lost during other types of operations.[223] The intravenous administration of aminoacetic acid, with or without the simultaneous ingestion of choline, failed to increase the urinary output of creatine or creatinine.[224] The failure is attributed to coexisting hepatic insufficiency. Elman,[225] in discussing the parenteral administration of fluids and food, stresses the value of intravenous administration of amino acid (in the form of a hydrolysate of casein) to prevent or correct protein loss when assimilation from the gastrointestinal tract is impossible. In complete starvation 100 Gm. of protein are lost daily. Elman estimates that 100 Gm. of dextrose is sufficient to reduce the protein loss two thirds and recommends as a basic formula the daily administration of 100 Gm. of dextrose and 50 Gm. of amino acids, to which addition dextrose protein, saline solution, vitamins and fluids may be added as indicated.

Benign Tumors.—Weinberg and Raider[226] discuss pedunculated tumors of the stomach and report a case in which the filling defect caused by the polyp was observed to vary between the stomach and the duodenum on different roentgenologic examinations. Centeno[227] found that 29 benign tumors of the stomach had been observed in Argentina between 1925 and 1942.

Lymphosarcoma. — McSwain and Beal[228] found that lymphosarcoma constitutes 1.9 per cent of the malignant lesions of the gastrointestinal tract. The differentiation from carcinoma was seldom made before histologic examination. Two suggestive diagnostic points on roentgenologic examination were the large size of the lesion in relation to the short duration of symptoms and the presence of whorl-like defects in the barium outline. Of 20 patients, 6 were alive without evidence of recurrence after surgical removal and 2 after roentgen therapy. The mortality was 42 per cent. The prognosis was most favorable for those for whom complete removal was possible. Roentgen therapy is advised in every case unless the lesion has been completely eradicated. In a series of 258 patients with initial diagnoses of gastric neoplasm Yarnis and Colp[229] found the correct final diagnosis for 8 (3.2 per cent) to be lymphosarcoma, seven of the lesions being typical small round cell tumors and one a reticulum cell sarcoma. The clinical picture was indistinguishable from that of carcinoma. The roentgenologic examination disclosed exaggerated folds and giant rugae. Gastroscopically the exaggerated rugae with ridgelike elevations and nodular or polypoid tumors were covered with relatively normal mucosa with very minimal ulceration. The authors question whether diffusely infiltrating nonulcerative lymphosarcoma is a surgical disease, for better results may be obtained by radiation therapy alone. The prognosis, however, is poor, for other authors have been able to collect only 26 five year cures in the entire literature of some 246 cases. Bassler[230] reports 4 cases of leiomyosarcoma. An enormous ulcer of the lesser curvature of the stomach,[231] found to be lymphosarcomatous when resected, is described. A 27 year old soldier was found to have a round cell sarcoma of the stomach.[232] A malignant lymphoblastic lymphoma of the stomach with

221. Ariel, I.; Rekers, P. E.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract, Ann. Surg. **118:** 366-371, 1943.

222. Rekers, P. E.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: VI. Disorders in Alimentary Digestion with Absorption in Patients Who Have Undergone Total Gastrectomy for Carcinoma of the Stomach, Surgery **14:**197-215, 1943.

223. Oppenheim, A.; Pack, G. T.; Abels, J. C., and Rhoads, C. P.: Estimation and Significance of Blood Loss During Gastrointestinal Surgery, Ann. Surg. **119:** 865-872, 1944.

224. Abels, J. C.; Kupel, C. W.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: XIII. The Effect of Glycine on the Urinary Excretion of Creatine and Creatinine, Especially by Patients with Cancer of the Gastrointestinal Tract, Cancer Research **4:**145-149, 1944.

225. Elman, R.: Parenteral Fluids and Food in Gastrointestinal Disease, Bull. New York Acad. Med. **20:**220-236, 1944.

226. Weinberg, T. B., and Raider, L.: Pedunculated Tumors of the Stomach Prolapsing Through the Pylorus, Radiology **41:**52-55, 1943.

227. Centeno, A. M.: Tumores benignos del estómago, Prensa méd. argent. **30:**2196-2206, 1943.

228. McSwain, B., and Beal, J. M.: Lymphosarcoma of the Gastro-Intestinal Tract: Report of Twenty Cases, Ann. Surg. **119:**108-123, 1944.

229. Yarnis, H., and Colp, R.: Lymphosarcoma of the Stomach, Gastroenterology **1:**1022-1039, 1943.

230. Bassler, A.: Leiomyosarcoma of the Stomach: Presenting Four Cases, Am. J. Digest. Dis. **10:**342-344, 1943.

231. Ayerza, L.; Chavarri, M. A., and Lellis, J. T. M.: Nicho gigante del estómago por linfosarcoma, Arch. argent. de enferm. d. ap. digest. y de la nutrición **19:** 197-201, 1944.

232. Porritt, A. E.; Hughes, K. E. A., and Campbell, R. J. C.: Sarcoma of the Stomach, Brit. J. Surg. **31:**395-398, 1944.

extension to the transverse colon and involvement of regional lymph nodes was encountered in a patient with a benign giant cell tumor of the left femur.[233] Doran and Doran [234] report a lymphosarcoma of the stomach with perforation into the gastrocolic omentum. Resection was followed by recovery.

Hodgkin's Disease.—Jungman [235] reports an unusual case of Hodgkin's disease of the stomach occurring in a 60 year old man who had experienced epigastric discomfort one hour before meals, relieved by food, for two months. Severe pain about the umbilicus followed the meal. Roentgenologic examination of the stomach showed severe hypertrophic gastritis with rigid folds extending from the cardia to the pylorus. Peristalsis was very sluggish and almost invisible at the middle part of the lesser curvature. The gastroscopic appearance suggested a widely infiltrated carcinoma. The pathologic report was Hodgkin's lymphogranuloma infiltrating all the coats of the stomach. Lahey [236] describes the most extensive operation ever undertaken in his experience, namely, total gastrectomy, splenectomy, omentumectomy, colectomy and resection of the left lobe of the liver. The operation was technically successful, although the patient died five months later from a recurrence diagnosed by the pathologists as Hodgkin's disease.

(To Be Concluded)

233. Case Records of the Massachusetts General Hospital, Cabot Case 30072, New England J. Med. **230**: 201-204, 1944.

234. Doran, W. T., and Doran, W. T., Jr.: Lymphosarcoma of the Stomach with Perforation: Gastric Resection with Recovery, Am. J. Surg. **61**:136-137, 1944.

235. Jungman, H.: Hodgkin's Disease of the Stomach, Brit. J. Radiol. **16**:386-387, 1942.

236. Lahey, F. H.: Total Gastrectomy, Splenectomy, Resection of the Left Lobe of the Liver, Omentumectomy and Colectomy upon One Patient in One Operation, Ann. Surg. **119**:222-224, 1944.